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Original Articles

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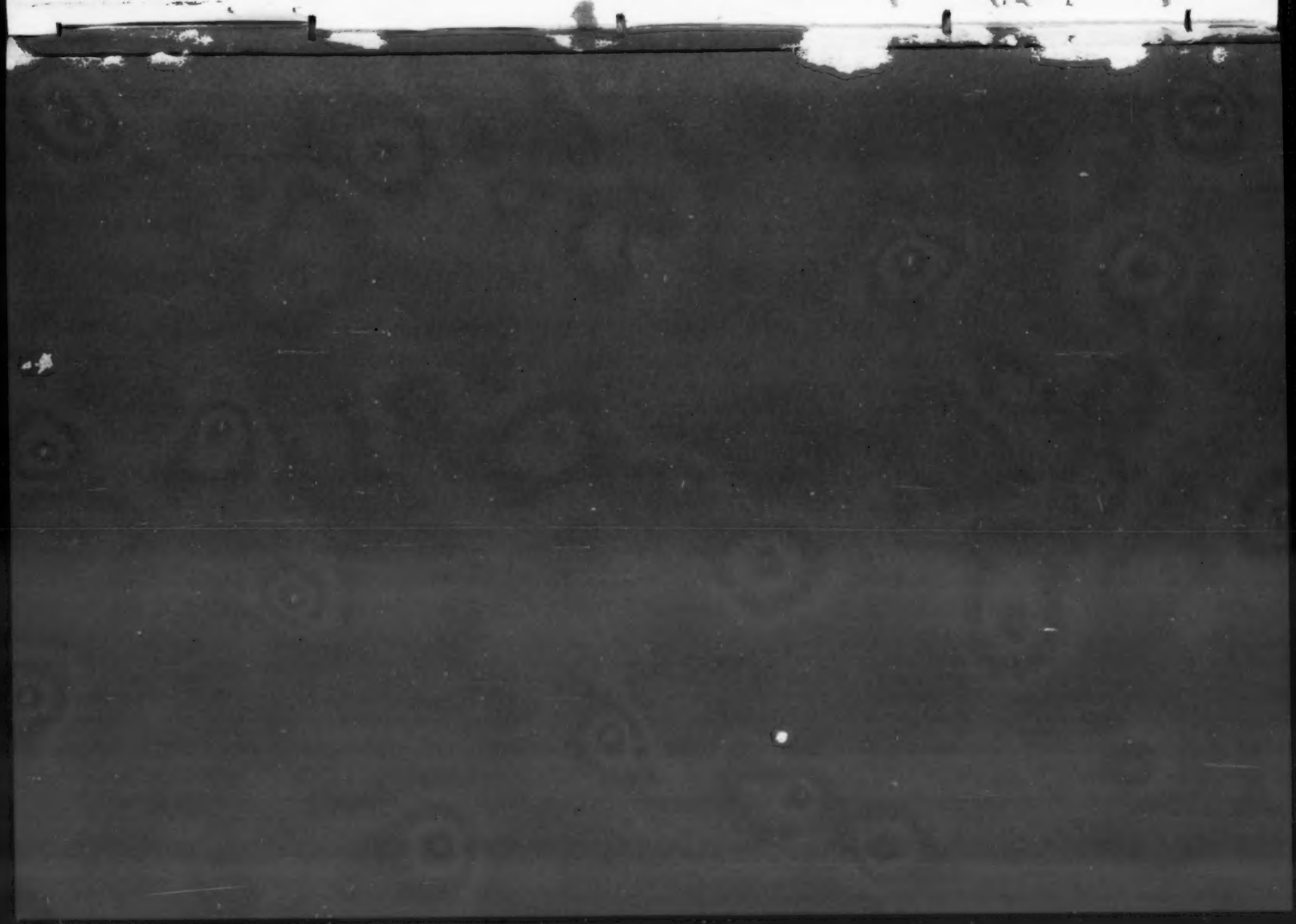

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MAY 1949

ADVANCES IN TREATMENT OF MALIGNANT DISEASE

*The Ludwig Kast Lecture**

C. P. RHOADS

Director Memorial Hospital Center for Cancer and Allied Diseases. Professor of Pathology, Cornell University Medical College, and Director of Sloan-Kettering Institute

THE search for chemicals to control cancer has followed a course much like the one pursued over the years by those who wished to transmute the elements. Every age has had its alchemists and every one its cancer remedy. The confidence of the credulous has been so repeatedly betrayed that it has recoiled from the repeated failures. A long series of bitter disappointments has led to a conditioned reflex: the view that all who search for new means of cancer control are idyllic dreamers, blissfully unaware of the impossibility of ever attaining their goal. In spite of alchemists and sceptics, however, transmutation is now a fact. Similarly, notwithstanding past failures, mistakes, and confusion, progress in cancer therapy now is being made. It is as yet an enormously ill-defined, vague, stirring and struggling of an amorphous mass of scientific facts, yet its tendency to take form and to move toward a definite goal is now both apparent and real.

The status of the struggle at present is seriously complicated, how-

* Presented October 4, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

ever, by recent observations[1-4] which, though they were not capable of confirmation, nevertheless indicated an important line of research. The study concerned a vitamin, a derivative of folic acid, scientifically known as pteroyl-gamma-glutamyl-gamma-glutamylglutamic acid, named by its manufacturer, teropterin. This play, though erroneous, was an enormously important development, since it has greatly aided definition of the true goal and possibly the means for attaining it. The folic acid story began with cancer, has gone through a long series of plots and counterplots, and now, in completely new form, with an O. Henry twist, is back on cancer again.

Claims for Folic Acid in the Therapy of Cancer

Beginning in 1939 there appeared a series of papers by Lewisohn, Leuchtenberger, and their associates, in which they described the ability of a number of different materials to cause the disappearance of spontaneous mammary tumors in female Rockland Farm strain mice. Certain of these materials, notably a spleen extract[5] and a barley extract,[6] were said to cure about 30 per cent of the treated animals. A similar rate of regression in untreated controls was not observed.

A yeast extract[7] was also described as effective, and efforts were undertaken to isolate its active principle in pure form. Inositol[8] was the only one of the crystalline vitamins of the B complex present in yeast which was alleged to be effective in inhibiting the experimental tumor.

The vitamin, pteroylglutamic acid (folic acid) was first described by Snell and Peterson[9] as a growth factor required by certain bacteria. Shortly afterward, Pollack, Taylor and Williams,[10] at the University of Texas, in assaying B complex vitamins in various tissues found the highest level in certain animal neoplasms.

In 1944, Lewisohn, et al.[11] reported that injections of a crude extract which had many of the properties of folic acid would inhibit in mice the growth of a transplanted sarcoma. A year later[12] they described cures of spontaneous breast cancers in three different strains of mice treated by daily intravenous injections of the same material. Subsequently, they stated that the same activity was shown by pteroyltriglutamic acid, a conjugate of folic acid, and that pteroylglutamic acid (folic acid) itself was without any value when tested under similar conditions.[13] This statement was remarkable since good evidence exists to prove that all the folic acid conjugates are broken down in mammals to simple folic

acid. This is indicated by the disappearance of all signs of deficiency of the vitamin and the recovery of folic acid from the urine of animals given the conjugates.

The development of synthetic procedures next made available in quantity, and in pure form, pteroylglutamic acid (folic acid), pteroyldiglutamic acid (diopterin), pteroyltriglutamic acid (teropterin), pteroylheptaglutamic acid (vitamin B_c conjugate).

Sugiura,[14] using material similar to that employed by Lewisohn, was unable to confirm the latter's observations. Rhoads[15] also failed in later experiments.

Lewisohn believed that the conditions observed in his laboratory had not been followed exactly by the groups which failed to obtain like results. Particular reference was made to the importance of daily injection of the material intravenously and by no other route, of preventing its inactivation by light, and of making open biopsies of the neoplasms. In general, those who tried to confirm the claims did their best to observe the conditions originally described, but in many instances differences of technique crept in. Later, however, Lewisohn reported that he could duplicate his results by feeding the pteroyltriglutamic acid (teropterin) and that injections were not required. The experiments of Rhoads were done without open biopsy since that procedure was found to result frequently in surgical cure of the soft, localized neoplasm unless precautions were observed.

While the work of Lewisohn was in progress, and during the war, an apparently wholly unrelated activity developed under the secrecy of the army research program on chemical warfare. A group of agents known as the nitrogen mustards, or B-chlorethyl amines, was found to have a profoundly toxic effect on both normal and neoplastic tissue of the hematopoietic system. Gilman and Philips[16] and Jacobson,[17] were leaders in this extraordinarily interesting enterprise. For the past four years an extensive program of distribution and of reporting on the effectiveness of the best of these compounds, HN_2 or methyl-bis (B-chlorethyl) amine, has been in progress under the National Research Council. Karnofsky,[18] who had this activity in charge, has recently reported. The summary of his report is so clear and unequivocal that I quote it here.

"Nitrogen mustard represents a new and valuable agent for the management of inoperable neoplastic disease. Methyl-bis (B-chloro-

ethyl) amine hydrochloride (HN_2), the nitrogen mustard in clinical use, is a systemically acting cell poison most closely related in its therapeutic effects to total body irradiation. Its advantages over total body irradiation are that it is less expensive, easier to administer, its toxic and therapeutic effects develop more quickly, tissue recovery is more rapid and its dosage can be more safely controlled so that maximum therapeutic doses are possible. Total body irradiation causes less nausea and vomiting, and its therapeutic effects may be more prolonged.

"HN_2 is an effective, temporary, palliative agent of irregular activity in Hodgkins' disease, lymphosarcoma, chronic leukemia, polycythemia vera, mycosis fungoides, primary lung carcinoma and, to a much lesser degree, in other miscellaneous neoplastic disorders. There is little evidence, however, that it alters the course of these diseases or appreciably prolongs life. Its great value is as an adjuvant to x-ray therapy in the palliation of neoplastic disease. X-ray therapy is more effective in treating localized disease. . . . HN_2 should be given only when definite indications exist. Because of its toxicity and unpleasant side-effects, its indiscriminate trial in patients with inoperable cancer or in terminal stage of the disease is entirely unjustified."

Studies of the mechanisms by which nitrogen mustard exerts its transient but perceptible effect upon some neoplastic tissues led to three interesting findings. The material was very active in arresting mitosis, a process which is the duplication of structures rich in nucleic acid. Exposure to nitrogen mustard of material such as Drosophila (fruit fly) or Neurospora (the mold), suitable for the study of genetic effects, revealed promptly that the chemical was very effective in causing mutations. This suggested, because of the prominence of nucleic acid in the structure of chromosomes upon which mutations depend, that the poison affects nucleic acid or some mechanism concerned with its production. Finally, it was learned that nitrogen mustard, in exceedingly low concentrations, inhibits the normal synthesis of cellular nucleic acid.

These findings, that the growth of certain neoplastic cells can be adversely influenced by a compound, nitrogen mustard, which interferes coincidentally with cellular structures containing nucleic acid and enzymes for forming them, were of great interest. They suggested that there might be found other tumor-inhibiting agents among those which inhibit nucleic acid metabolism.

The next development came in observations based, it is stated, upon a critical analysis of the data of the Lewisohn group. Farber and his associates[1] reported studies of ninety patients with malignant disease. Both pteroyldiglutamic acid (diopterin) and pteroyltriglutamic acid (teropterin) were used in an effort to establish the therapeutic value of these compounds in treatment. No evidence of toxicity was found, and improvement in energy, appetite, and sense of well-being was noted. It was believed that this could be ascribed in many—but not all—instances, to a psychological effect only; to the improved morale resulting from institution of a potentially-useful therapeutic procedure. In a few instances, diminution of pain also was reported.

It was stated in the report that in a few cases a causal relationship was apparent between the administration of the glutamic acid compound employed and objective evidence of change in the patient's condition or the histological appearance of the tumor.

In a larger group of patients in which conventional therapeutic agents, such as irradiation therapy, were also employed, changes were observed under conditions which suggested that it was the addition of the glutamic compound (teropterin) which played an important part in their appearance. As examples of these changes, reference was made to temporary decrease in the size of subcutaneous nodules of an amelanotic carcinoma, temporary decrease in the size of metastases to the lung from a carcinoma of the testis, two instances of necrosis seen on pathological examination of tumors, and two drops in acid phosphatase level in one patient with carcinoma of the prostate gland.

Farber concluded that further investigation of pteroyltriglutamic acid (teropterin) was justified from the data obtained. The implication is clear that the authors felt that a real therapeutic effect had been exerted irregularly on the course of the neoplasms subjected to study.

Somewhat later, in a symposium conducted by the New York Academy of Sciences, Klainer[2] described improvement in a patient with metastatic carcinoma of the breast treated with pteroyltriglutamic acid (teropterin) and also given testosterone. Lehv and his associates[3] reported the results of the administration of pteroyltriglutamic acid (teropterin) to twenty patients with cancer. Relief of pain and sense of well-being were reported, but there were no objective changes in the lesions.

Meyer,[4] in a paper given at this same symposium, reported both

subjective and objective improvement in 12 patients with neoplasms of the hematopoietic system treated with pteroyltriglutamic acid (teropterin).

Simultaneously, in the same communication, and concerning the same types of neoplasms, Meyer reported beneficial results of exactly the same, or pteroyltriglutamic acid (teropterin) induced type, brought about by two compounds which function wholly as antagonists, or neutralizers, of pteroylglutamic acid (folic acid). These are also presumably antagonists of pteroyltriglutamic acid (teropterin), since that compound functions as folic acid in the mammal and is converted to that compound.

In the same symposium Woll[19] reported that Rous sarcoma of chicks could be prevented by maintaining the birds on a diet free of folic acid by administering three folic acid antagonists, 4-amino folic, 4-amino folic with d(−)glutamic and 4-amino pteroylaspartic acid. Furthermore, once the tumor had developed, the antagonists would prevent further growth.

Thus in a noteworthy symposium, both folic acid and its antagonists were advocated simultaneously for the control of cancer, an anomaly which aroused widespread attention.

Earlier, Spies,[20] Davis,[21] Doan[22] and, later, Lawrence,[23] all reported their failures to influence neoplasms of hematopoietic tissue in any way with pteroylmonoglutamic acid (folic acid).

Following these reports, both pteroyldiglutamic acid (diopterin) and pteroyltriglutamic acid (teropterin) were distributed by the manufacturer to at least 225 investigators. These were then circularized by letter to ascertain the results they obtained by the use of the compounds. Their reports are recapitulated in a report of the Council on Pharmacy and Chemistry of the American Medical Association.[24] The summary states that the facts available from this questionnaire do *not* yet support the view that pteroyltriglutamic acid (teropterin) has an anti-cancer effect. The method employed to assess the value of the preparation is criticized.

It is the considered opinion of many that the subjective relief referred to by some of those who answered the questionnaire could have been entirely the response to suggestion. This sort of response has been reported for many years in countless studies of inert material administered to patients with cancer.

Therapy of Neoplasms by Antagonists of Folic Acid

The important role of folic acid in hematopoiesis was first demonstrated by Spies[25] for macrocytic anemia and by Darby and Jones[26] for sprue. Their observations were rapidly and amply confirmed. They were in accord with the fact that, in animals, the induction of a folic acid deficiency by withholding that compound from the diet results in anemia and leukopenia.

The principle of anti-metabolite effect first established by Woods[27] for the sulfonamides and extended by Woolley[28] suggested an interesting possibility for the induction of a folic acid deficiency. This would require the preparation of compounds so similar to folic acid that the cells would take them up as folic acid but at the same time so dissimilar that they could not function as folic acid in cellular life.

The first antagonist to folic acid was d(−)methyl folic acid synthesized by Martin and his associates.[29] Its effect was demonstrated by its ability to inhibit the growth of S. fecalis R and the fact that pteroylglutamic acid (folic acid) would overcome this inhibition.

In 1947 Franklin, Stokstad, and Jukes[30] described the acceleration of a pteroylglutamic acid deficiency in mice and chicks by a crude chemical antagonist. The active component of the crude preparation may be 7-methyl-pteroylglutamic (L) acid. Slow growth, anemia and leukopenia were caused and pteroylglutamic acid (folic acid) prevented the appearance of the syndrome. In 1948 the same authors[31] reported the toxic effects of feeding a new antagonist prepared in pure form, 4-amino-pteroylglutamic acid (aminopterin), to mice. This material had previously been shown to act as a folic acid antagonist in inhibiting the growth of S. fecalis R since the effect was reversed by increasing the level of pteroylglutamic acid in the medium. In the experimental mice, some depression of blood values as a sign of folic acid deficiency was effected by the 4-amino-pteroylglutamic acid (aminopterin), but although reversal of the toxic effect by pteroylglutamic acid (folic acid) was observed at certain levels of dosage, this could not be demonstrated at higher levels.

The next development was the report by Farber and his coworkers[32] of temporary remissions induced in acute leukemia in children. These remissions followed the use of the folic acid antagonist, 4-amino-pteroylglutamic acid (aminopterin). It is of interest that the

term "antagonist" was used, even though in mice the toxic effect of this compound could only be reversed by the administration of folic acid within a very narrow range of dosage.

In his communication, Farber reports an "acceleration phenomenon" in the leukemic process seen in the marrow and viscera of his children with acute leukemia treated by the injection of the folic acid conjugates, pteroyldiglutamic acid (diopterin) and pteroyltriglutamic acid (teropterin). This is not referred to in his original publication[1] on the use of these materials in the treatment of patients with neoplastic disease.

Since the disease was accelerated or made worse by folic acid, and since other leukotoxic agents, such as the nitrogen mustards, have a harmful effect upon the pathologic leukocytes of leukemia, as well as upon normal ones, and since a folic acid deficiency inhibits leukocyte formation, a trial of the therapeutic value of a deficiency induced by folic acid antagonists was undertaken.

Studies on fourteen children with acute leukemia treated with the folic acid inhibitor, pteroylaspartic acid, and seven treated with methyl pteroic acid are referred to, but it is stated that the results will be reported in another publication.

Sixteen children with acute leukemia were given the 4-aminopteroylglutamic acid (aminopterin). Of these sixteen, ten were reported as showing clinical, hematological, and pathological evidence of improvement of an important nature of three months' duration at the time of the publication. Six showed no response. Of the ten patients who were favorably affected, five are reported on in detail and it is stated that the courses of the others were essentially similar. Distinct improvement, well-sustained, clearly followed the administration of aminopterin to these five children. It should be noted, however, that of the five cases reported, two showed spontaneous remissions without treatment, and two of the remissions which followed treatment were not wholly complete.

In a later communication Heinle and Welch[33] described rapid hematologic relapse following the administration of pteroylglutamic acid (folic acid) to three patients with chronic leukemia. They reasoned, like Farber, that since pteroylglutamic acid (folic acid) made them worse, a deficiency of it should make them better. An effort to induce a deficiency of pteroylglutamic acid (folic acid) in one of these pa-

tients by a diet low in its content of that substance, combined with the administration of a crude antagonist and an intestinal bacteriostatic, was followed by a drop in the leukocyte count and the death of the patient.

The most recent published statement on this subject is an editorial in the journal *Blood*.[34] This investigator reports the occurrence of 4 remissions in his series of 16 adults with acute and sub-acute leukemia treated with 4-amino-pteroylglutamic acid (aminopterin). He speaks of a "distinct improvement" of the marrow picture, a rise in red cells and platelets and also refers without detail to one remission in a case of leukemia in childhood. The statement is made that the factor of spontaneous remission can be completely ruled out in his own and in Farber's series of cases.

Farber[32] mentions the stomatitis which can be a serious toxic complication of the use of 4-amino-pteroylglutamic acid (aminopterin). The *Blood* editorial also refers to personal communications from various centers where that drug and related materials are being used. They indicate, it is said, that the results have often been disappointing, and that adverse reactions such as hemorrhage or aplastic anemia are common.

In any discussion of the results of the use of a potentially active therapeutic compound in the treatment of leukemia, either in adults or in childhood, a precise definition of the term "remission" is required. Furthermore, careful comparison of the results should be made with the course of the disease in a like number of untreated patients of similar types. It is not proper, in the opinion of many, to apply the term "remission" to a simple decrease in the number of pathological leukocytes in the circulating blood, even though this be associated with some decrease in the number of blast forms, but not their disappearance, and with evidence of decrease, but not absence, of other manifestations of the disease. Rather, perhaps "improvements" should be the word applied to incomplete trends toward health.

Fluctuations are known to be a feature of untreated leukemia, even the acute disease. Transfusions, required so frequently, are probably a contributing factor here since they are often followed by profound symptomatic response.

The term "remission" properly should be reserved for an essentially complete restoration of normal hematologic function and health

in all other respects. It is not applied to a simple leukotoxic effect, such as can be exerted by a number of agents, without essentially complete disappearance of all manifestation of disease. As mentioned previously in the five patients whose records were reported by Farber,[32] two showed periods of spontaneous remission while untreated, and in two the remission was incomplete as far as is indicated by the data presented.

In a series of seven children with acute leukemia treated by Burchenal[33] at the Memorial Hospital, two showed remissions, which could be ascribed to the folic acid antagonist used in therapy. In the remaining patients, in no instance did more than a transient and partial improvement of blood levels result from aminopterin therapy. Furthermore, toxic effects were distinct with a tendency to hemorrhage and evidence of gastro-intestinal irritation.

To establish clearly, then, the role of anti-folic therapy of acute leukemia in children is very difficult at the present time. Several workers have presented evidence that it is of value in inducing remissions irregularly but sufficiently often to be a matter of very great interest and importance. More data are urgently required.

Studies of the effect of the administration of folic antagonists, principally 4-amino-pteroylglutamic acid (aminopterin), have been made by Burchenal[33] in an extensive series of adults with myeloid leukemia, and a few patients with other neoplasms of the hematopoietic system. In chronic myeloid leukemia, a leukotoxic effect with a drop in leukocyte count to more normal levels can be exerted regularly. This is not infrequently associated with a decrease in size of involved organs but rarely with a subsequent restoration of full erythropoietic activity. In general, however, these salutary results are not seen unless the drug is pushed to the point of distinct and possibly serious toxicity. The periods of improvement which follow are usually not complete remissions, though these do occur.

Aminopterin is an experimental drug of great interest. In man, however, except possibly in acute leukemia in children, there is little differential between its effect on neoplastic compared with normal cells. That it has an injurious action on the leukocytes of leukemia is a fact beyond question, but more data will be required before we can conclude that it will regularly restore the patients to health.

Tests have been made at the Memorial Hospital, Sloan-Kettering Institute, in very great detail on the effect of folic acid antagonists on

the course of neoplasms in animals. These tests reveal that great care must be used in setting up the experiments and in evaluating the results. Certain cardinal points must be borne in mind. The first is that results must be expressed in terms of a ratio between the primary toxicity of the compound employed and the inhibition of tumor growth effected. It is not enough simply to state that one compound is less or more toxic than another. The second principle is that a spectrum of different tumors of varying sensitivity must be employed in testing, since there is very considerable variation in their response to growth-inhibiting agents. Finally, response of the tumor in terms of cytological injury must be compared with that of the tissue in the body most sensitive to inhibition of growth, notably the lymphatic tissue and the bone marrow. The desired end in all such experiments is to establish clearly a preferential injurious effect on the neoplastic, as compared with any normal, cell.

If these criteria be applied to the use of aminopterin in animals, as its effects have been observed in an elaborate and extensive series of studies, the fact is apparent that, as in man, the agent has a profound leukotoxic effect, but not a strong differential or preferential toxicity for neoplastic over normal cells. Partial regressions of certain sensitive experimental tumors of mice and rats can be obtained by the administration of aminopterin in doses sufficiently near the tolerated level so that some of the animals are killed by the therapeutic agent. If a dose level is maintained which can be tolerated by the animals without fatality for a period of seven days, it is extremely difficult to establish clearly any profound inhibitory effect of the compound on tumor growth, and certainly none which is not associated with evidence of bone marrow injury. Similar results have been attained in limited experiments on patients.

In experimental animals the use of the 4-amino-N^{10}-methyl pteroylglutamic acid (a-methopterin)[36] is associated with more definite evidence of a restraining effect upon the growth of neoplastic tissue. With this compound, both in experimental leukemia in mice and in transplanted sarcoma 180, a well-defined inhibition of growth of the neoplastic cells can be demonstrated at dose levels which are well under those which are tolerated by the animals. There is a suggestion, furthermore, that in human beings some objective evidence of growth restraint of sensitive neoplasms can be obtained, although much further

data will be required before any final conclusion is justified.

The experience of Memorial Hospital, Sloan-Kettering Institute, with aminopterin and a-methopterin can be summed up with the statement that the first compound seems to have little preferential injurious effect on neoplastic, compared with sensitive normal, cells. The second, however, seems to exert some preferential injurious action on certain types of sensitive neoplasms.

The work presented is one of the most interesting studies now under way in the pathologic physiology of neoplasms. It is of no great moment today whether this or that compound has perceptible–or more than perceptible–effects on leukemia. It is of very great moment, however, that in the field of compounds which may well interfere with the formation or metabolism of nucleic acid, substances are at hand which poison certain neoplastic cells, even though this effect be a weak one.

A mass of studies indicate that the cancer cell in general contains more nucleic acid than does its normal analogue. The agents which cause cancer are those which induce mutations by their effects on nucleic acid-containing structures, the chromosomes. Certain viruses, and other self-reproducing agents capable of exerting profound effects upon the nature of cells, are nucleic acid in nature. What would be more reasonable than to find that the fundamental difference between normal and neoplastic cells resides in the nucleic acid of which the templates for our bodily manufacture of cellular material is composed. And if this difference is there to be found it is quite likely to be done by the demonstration of a differential effect of a nucleic acid precursor on normal, as compared with cancer, cells as by any analytical method. Studies of this type compose, indeed, the procedure of empiric analysis through differential inhibitions, by which many great discoveries have been made.

Great honor is due those who, step by step, have battered out the links in the long chain of discoveries which have bound cancer research with fundamental aspects of nutritional biochemistry. How surprised would Miescher be, were he alive in this, his 104th year, to learn that his isolation of nucleic acid from fish sperm and its characterization would be the first step toward a better understanding of the cancer cell.

It is apparent from the studies which have been made that no millennium in cancer chemotherapy has been attained by the use of any

anti-folic material so far described. Nor, indeed, is any generally useful agent yet at hand. It is equally apparent, however, that a most important field for investigation has been opened up to study. With the great variety of analogues of folic acid and related compounds which can be prepared synthetically in the laboratory and the reliable methods of assay available, it may be hoped that materials showing a greater preferential toxic effect to neoplastic cells will be obtained in the future.

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RESULTS OF OPERATIONS FOR HYPERPARATHYROIDISM*

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THE first operative cure of generalized osteitis cystica fibrosa by removal of a parathyroid adenoma was reported by Mandl[1] in 1925, just under a quarter of a century ago. Since then, and mostly in the past 15 years, several hundred cases have been operated upon with success and many articles have been written discussing the physiological principles involved, the differential diagnosis and operative technique. Norris[2] two years ago in a review of the literature found 254 operated cases, which he included in his interesting article that deals largely with the embryology of the parathyroid glands.

It seemed to us that it might interest you to have a summary of the 32 cases operated on at the Presbyterian Hospital. A few of these have been reported previously,[3,4] and some were operated on by Hanford, Elliott and Self, who have kindly allowed me the privilege of including their cases with my own.

Inasmuch as prognosis is the main thing of interest to the patient after relief from symptoms has been achieved, our cases will be presented to you including the follow-up results, which bear a distinct relation to the stage of development of the disease at the time of operation. No disease entity can be subjected to a rigid classification, but it is useful in considering hyperparathyroidism to keep in mind its two important ill effects, namely, skeletal deformity and particularly renal damage. Operation prior to the inception of either of these will have a brilliant result. Operation after either has occurred will not eliminate bony deformity nor will it affect renal damage that has become irreversible. This fact re-emphasizes the value of early diagnosis, and the vital importance of considering the possibility of hyperparathyroidism being present when any of its symptoms are noted that

* Read January 6, 1949 at the Annual Meeting of The New York Academy of Medicine. From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

TABLE 1—NO RENAL IMPAIRMENT. NO CALCULI

Case	Sex Age	Duration	Symptoms	Ante-Op. Ca.	Ante-Op. P.	Ante-Op. P'tase	Site	Size	Wt. Gms.	Tetany	Follow-Up
F.G. 608926	F 43	1 yr.	G.I. Pain. Polyuria Wt. loss.	12.9	1.7	84.4	L.U.M.	5.2 x 1.2 x 1.9	4.0	0	Kyphosis. O.K. 8 yrs.
L.D. 897066	F 44	3½ yrs.	Back pain. Fatigue. Nervous.	12.1	2.1	49.0	L.L.	3.3 x 2.0 x 0.8	3.65	+	O.K. 1 yr.
*A.B. 742845	F 21	5 mos.	Pains.	14.5	2.3	37.0	L.L.	4.0 x 3.5		+	O.K. 3¾ yrs.
*E.D. 737265	F 41	1 yr.	Polyuria Fracture. G.I. Pain.	17.4	2.6	10.8	L.L.	4.0 x 5.0	27.0	Ca. 4.9 +	Bowing femora. O.K. 4½ yrs.
K.B. 892801	M 44	1½ yrs.	Polyuria G.I. Fatigue.	13.6	2.8	8.1	L.U.M.	2.2 x 1.9 x 1.2		0	Asymptomatic. T 9 compressed. O.K. 1 yr.
****L.L. 491999	F 53	?	Paget's. Diag. on Chem.	11.8	2.3	35.8	L.U.	2.5 x 1.5 x 1.1		0	Paget's progressing. Ca. 9.6 at 12 yrs.
B.N. 480103	F 63	5 yrs.	Pains. Weak. Deformity.	12.8	1.9	11.6	L.U.M.	2.2 x 1.2 x 0.5		Ca. 6.6 +	Deformed but walking and works at 10⅓ yrs.
**R.LaR. 766057	F 29	3 yrs.	Pain. Weak.	13.2	2.1	23.3	L.U.	3.2 x 1.8 x 1.5	4.0	+	Caesarean at 1 yr. O.K. 3 yrs.
F.D. 428858	F 76	? yrs.	Vague G.I. Fatigue	15.1	2.7	12.3	R.L.	5.0 x 3.2 x 1.5	12.9	+	O.K. 12 yrs.

*Operator: J. M. Hanford.
**Operator: R. H. E. Elliott.
****Previously reported (3).

cannot be adequately explained on another basis. Such complaints as lassitude and fatigue, polyuria, indigestion, as well as vague muscle and bone pains may be present for months before a spontaneous fracture or bony swelling occurs, and of course all cases of renal colic should be immediately suspect.

Our 32 cases fall into four main clinical groups with calculus formation, or calcification within the kidney substance, with or without renal damage, as the significant elements. Bony deformity is naturally of great importance to the patient but is not important clinically as far as postoperative restitution of normal physiological calcium and phosphorus balance is concerned. One group of nine patients had neither calcium deposition nor renal impairment, twelve presented calculi, or a history of having passed one or more stones, or renal calcification without any definite impairment of renal function, whereas eleven could be classified as showing renal damage. Of these eleven, five were borderline, with high normal nitrogen retention and low normal P.S.P. excretion rate, the other six presented evidence of serious renal insufficiency. It is interesting to note that all but one of this group of eleven with renal damage had well marked deposition of calcium either within the kidney or as frank urinary calculi. Thus, out of the entire group of 32 individuals there were 22 (68 per cent) who came in with a history of having passed one or more calculi, had renal or ureteral calculi present, or showed definite x-ray evidence of calcification within the kidney substance.

The follow-up results at intervals from a few months to twelve years bear out the thesis that renal function at the time of operation determines the prognosis as to life expectancy. Moreover, all cases showed an immediate return to normal calcium and phosphorus levels, except after the second operation on one case of recurrent carcinoma and one of multiple tumors. There was no immediate operative mortality, but five patients died later of renal insufficiency and one died of recurrent functionating carcinoma of the parathyroid. Table I, which includes those with good renal function and no calculi, is of interest in that all but three complained of pains of a more or less vague type before deformity or fractures appeared. One of these (K.B.) has an asymptomatic compression of T 9; another (L.L.) in whom hyperparathyroidism was discovered in the course of frequent blood studies, has had Paget's disease of long standing,[3] and the third

TABLE II—RENAL CALCULI WITHOUT DEFINITE RENAL IMPAIRMENT

Case.	Sex Age	Duration	Symptoms	Ante-Op. Ca.	Ante-Op. P.	Ante-Op. P'tase	Site	Size	Wt. Gms.	Tetany	Follow-Up
****M.B. 521397	F 55	13 yrs.	Small stone. Repeated fractures.	12.8	1.9	2.7	U.M.	3.0 x 1.2 x 0.5		0	Cripple but O.K. at 10 yrs.
D.G. 546806	F 50	7 yrs.	Weak. 1 stone. Polyuria. Emotional.	11.2	2.7	30.3	L.L.	4.0 x 3.0 x 1.5	11.0	Ca. 5.5 +	O.K. at 9 yrs.
A.W. 532131	M 35	17 yrs.	Bilateral calculi.	13.0	1.2	3.8	L.U.	1.9 x 0.8 x 0.4	0.5	?	Gout. O.K. at 9 yrs.
**R.M. 750663	F 32	2 yrs.	Weak. Nervous. 1 stone.	12.4	2.4	24.0	L.L.	2.5 x 1.5 x 1.3		+ +	Chvostek 3 yrs. with normal Ca. Hypertension with preg. at 3½ O.K. at 4 yrs.
B.S. 567090	M 56	10 yrs.	Calculi. Pain. Weakness.	18.6	3.2	33.9	L.L.	4.5 x 4.5 x 3.2		Ca. 5.9 +	Carcinoma. Chem. O.K. 18 mos. Recurred.
B.S. (2 yrs. later)	58	6 mos.	Pain. Wt. loss. Polyuria.	19.1	3.1	23.0	2 ant. neck.	1.5 diam.		0	Post-op. Ca up. Down-hill course. D. 5 yrs. after 1st op.

Table II—(*Continued on next page*)

Table II—(*Continued from preceding page*)

N.L. 735037	F 38	1½ yrs.	Pain. G.I. Wt. loss. 20 lbs.	15.9	2.2	15.2	L.	2.6 x 2.5 x 1.7	5.9	+	3 ops. for calculi. O.K. at 9½ yrs.
N.M. 868500	F 42	3 yrs.	Fractures. Weak. Colic.	17.9	3.0	5.4		1.8 x 4.0 x 1.5	4.7	0	Ops. for calculi—bowing femur. O.K. 1½ yrs.
E.R. 662891	F 50	14 mos.	Calculi. Weak. Pains.	12.9	3.3	3.8	L.U.	1.7 x 0.6 x 0.3	0.16	0	O.K. 1 yr.
***F.E. 682482	F 45	3 yrs.	Pains. Wt. loss. Passed calculi.	15.8	2.3	34.2	L.U.M.	3.0 x 2.3 x 1.3	7.0	Ca. 5.6 +	No residual calc. O.K. 6 yrs.
***R.I. 672708	M 37	6 yrs.	Bilateral calculi.	12.3	2.0	3.5	L.L.	2.2 x 1.5 x 0.9		+	Renal colic. O.K. 5½ yrs.
**W.S. 841995	M 27	3 yrs.	G.I. Weak. Calculi. Fracture.	18.0	2.5	6.2	L.S.	3.0 x 2.3 x 1.8	5.2	+	Ops.: Femur; papillary thyroid carcinoma. O.K. 2 yrs.
O.L. 583499	M 40	4 yrs.	Pyuria. Renal colic.	14.1	1.4	10.1	R.L.	2.5 x 2.0 x 1.2		+	O.K. 9 yrs. Pyuria.

**Operator: R. H. E. Elliott.
***Operator: E. B. Self.
****Previously reported (3).

TABLE III—BORDERLINE RENAL DAMAGE

Case	Sex Age	Duration	Symptoms	Ante-Op. Ca.	Ante-Op. P.	Ante-Op. P'tase	Site	Size	Wt. Gms.	Tetany	Follow-Up
F.C. 874519	F 49	9 mos.	Colic. G.I. Scoliosis. Fracture.	14.8	3.3	28.1	R.L.	4.0 x 2.5 x 2.0	6.5	+	Continuing pyuria. Chem. O.K. at 1½ yrs.
****A.G. 782704	F 55	8 yrs.	Nephrectomy. Wt. loss. Colic. Pains.	13.4	1.4	25.0	R.L.	4.0 x 2.5 x 1.1		+	Carcinoma rectum, op. 10 yrs. O.K. at 12 yrs.
***R.E. 684467	M 29	10 yrs.	42 calculi passed. Several ops.	11.8	2.4	2.9	L.S.	1.5 x 0.9 x 0.4	0.45	+	O.K. at 1⅓ yrs.
A.N. 650235	F 53	11 yrs.	Multiple calculi.	12.6	3.0	3.1	R.L.	1.8 x 0.8 x 0.6		0	Several ops. for calc. O.K. at 6½ yrs.
***T.C. 713533	F 50	2 yrs.	Fractures. Bone pain. Nephritis.	10.6	2.0	43.1	L.U.M.	3.5 x 3.0 x 1.3	13.0	0	No post-op. tetany. Ca 6.4 O.K. at 5 yrs.

***Operator: E. B. Self.
****Previously reported (3).

(F.D.) was diagnosed during studies for supposed cholelithiasis. All of these patients are living with normal blood calcium levels at intervals from one to twelve years, in some cases with deformity but even so with improved general body function.

In Table II are listed those with calcium deposition but without renal damage. In this group there are two cases worthy of particular attention. Patient M.B. had been almost bed-fast for ten years because of her marked deformities due to repeated spontaneous fractures. She is still crippled ten years later but is not in pain and has suffered no renal impairment. Another patient in this group (B.S.) died five years after his first operation and three years after his second for carcinoma of the parathyroid. He had a large tumor with characteristic blood chemistry and x-rays; showed postoperative tetany with a drop of his serum Ca to 5.9 and did excellently for eighteen months. He returned after six months of pain and weight-loss, again with hypercalcemia and an elevated phosphatase. At the second operation two tumors were found in the muscle layers which were considered as possibly implants seeded at the time of the first procedure. No other tumors were found but metastasis must have occurred as no improvement in blood calcium level followed operation and his course was steadily down-hill, in spite of radiotherapy, to his death three years later.

Table III lists five patients with calculi and borderline renal impairment. In these individuals nitrogen retention was at the upper limits of normal and P.S.P. excretion rate was at low normal levels. Unquestionably, at some date these patients might have developed serious renal damage, but it is interesting to note the long duration of symptoms in this group, namely, 2, 8, 9, 10 and 11 years. One of them was a young man aged twenty-nine, who had passed forty-two calculi, but the others were around fifty years of age and it is not clear why their kidneys stood up so well. One of them (A.G.) who was reported in 1938[3] had an abdominoperineal resection of the rectum in 1946 and is still doing well in spite of the fact that she lost one kidney many years ago and has a calculus in the remaining kidney. Patient A.N. has had several operations for ureteral stone but is doing well nearly seven years after operation. In none of our cases has there been any suggestion of solution of calculi following the restoration of a normal blood calcium level. New stones have not been formed, apparently, but those already present have remained unchanged.

TABLE IV.—WELL MARKED RENAL DAMAGE

Case	Sex Age	Duration	Symptoms	Ante-Op. Ca.	Ante-Op. P.	Ante-Op. P'tase	Site	Size	Wt. Gms.	Tetany	Follow-Up
****M.W. 345901	F 52	15 yrs.	G.I. Calc. Kyphosis.	13.0	6.0	20.0	R.I.	3.0 x 2.0 x 0.8	4.5	+	O.K. at 2 yrs. Rising N.P.N. D. at 4 yrs.
****C.G. 384613	M 34	2 yrs.	Polyuria. G.I. Weak. Fracture.	15.4	2.5	34.8	R.I.	2.7 x 1.6 x 1.0	3.5	+	Renal calcific. O.K. at 4½ yrs. Rapid uraemia. D.
M.S. 432444	F 50	1½ yrs.	G.I. Colic.	13.0	2.9	4.4	R.S.	1.6 x 1.0 x 0.4	0.71	0	Progressive renal insuff. High B.P. D. 2 yrs.
***M.R. 423516	F 44	11 yrs.	Renal calc. Nephrectomy.	14.9	6.5	16.7	R.I.	4.5 x 3.8 x 2.2	17.0	+	Same as above. D. 18 mos.
***H.K. 713224	F 36	2 yrs.	Pains. Fracture.	14.1	3.1	7.6	L.U.M.	4.5 x 4.0 x 2.5	36.0	0	Renal calcific. Rising N.P.N. and B. P. at 5 yrs.
E.G. 832349	M 28	2 yrs.	Nephritis. Fractures.	14.2	2.5	12.9	L.	Sev. small.		0	O.K. 22 mos. Pain. Polyuria.
E.G. (2 yrs. later)	30	2 mos.	No calc. Weakness. Polyuria	12.1	5.5	23.5	R.U.	2.7 x 1.5 x 1.7	3.06	+	Renal insuff. increasing at 6 mos.

***Operator: E. B. Self.
****Previously reported (4).

Table IV contains the data on the patients with serious impairment of renal function. All of these except E. G. had renal calculi or calcification. In one patient (C.G.) there was massive calcification throughout a horseshoe kidney.[4] He exhibited moderate nitrogen retention, his P.S.P. excretion was satisfactory, but he showed constant albuminuria and low specific gravity. He did excellently for a period of four years and then began to show hypertension and rising nitrogen retention. Six months later he was admitted in uremia and made a rapid exitus. At postmortem all the remaining parathyroids which had been apparently normal at operation now showed typical secondary hyperplasia. His kidney showed extreme arterio-and arteriolar sclerosis, renal atrophy, and extensive calcification largely in the tubular area. Here and there were relatively normal glomeruli, so his renal failure was definitely on a quantitative as well as qualitative basis.

Two of the patients in this group gave long histories, one of eleven and one of fifteen years' duration, but the others had noted symptoms for two years or less. One of these (E.G.) was the only patient to present multiple small adenomata. His history began with discharge from the Navy because of nephritis. Later he suffered spontaneous fractures of the femur and patella and had one fruitless exploration of his neck at another hospital. Being unsatisfied with some small suspicious nodules behind the left lobe, we split his sternum and removed the tissue in the thymic area. Four small adenomas about 0.5 cm. in diameter were found in the specimen. On this admission he showed a B.U.N. of 24, a P.S.P. excretion rate of 20 per cent, and concentration to 1.011. He exhibited postoperative tetany and for a year and a half showed marked improvement in general well-being, with blood chemistry normal and definite recalcification in his skeleton. For 3 months before his second admission he noted weakness and polyuria and a rising blood calcium was found. At the second operation a tumor measuring 2.7 x 1.5 x 1.7 cm. and weighing 3.065 gms. was found embedded in the right lobe. On this admission his B.U.N. had risen to 90, his P.S.P. excretion was only 10 per cent and his concentration was only to 1.010. No suggestion of carcinoma was found, the tumor being a characteristic arrangement largely of rose red cells. He showed moderate tetany postoperatively; his calcium eventually falling to 9.6; but his strength has not improved; he looks badly and at 6 months is exhibiting progressive renal insufficiency from which

TABLE V.—ALL 32 CASES

Cases	*Renal Damage*	*Calc.*	*Good F.U.*	*Living Ill*	*Died Later*	*Normal Chem. Balance*	
						Temporary	*1-12 Yrs.*
9	0	0	9				9
12	0	+	11		1	1	11
5	?	+	5				5
5	+	+		1	4		5
1	+	0			1	1	

34 Operations, Mortality 0.

22 Calculi or Calcification—68%

Excellent Results 1-12 Yrs. in Re. Blood Chemistry—93%

Temporary—100%

he will eventually die. Since writing the above, a letter has been received from his doctor to the effect that pains are increasing and that x-rays show further progression of his disease but no data on blood chemistry or renal function are available. The clinical problem in his case is: Has he one or more other functioning tumors; is he developing secondary hyperparathyroidism; and, in view of his serious renal situation, can we offer him anything by another search of his neck? Our experience with secondary hyperparathyroidism due to severe renal insufficiency is completely discouraging. I am sure we must re-admit him for evaluation as to the possibility of re-operation, discouraging as the outlook may be. Fortunately, the occurrence of multiple adenomata is as rare as diffuse primary hyperplasia but both do occur and require early diagnosis, perhaps more vitally even than in cases of a single adenoma. The problem at operation is also far more difficult as the tumors may be extremely small and may be scattered about. In this particular case a small tumor had been removed at the first operation from near the site where the larger tumor was discovered two years later embedded in the thyroid. Probably it was so small two years previously that it was not discovered, being embedded in a sulcus of the thyroid.*

* On the day after this paper was presented a letter was received stating that E.A. had died two days previously without post mortem examination.

As another example of severe renal insufficiency, patient M. R. had lost one kidney and at the time of operation had an N.P.N. of 75 with P.S.P. excretion of 7.5 and ++++ albuminuria. She died 18 months later of progressive renal disease. Obviously the results in this group are disappointing but most of them had several years of relative comfort, which makes the operation worth while even in the face of grave renal disease. With the exception of E.G., hypercalcemia did not reappear in any case in this group.

Table V summarizes these 32 cases. Note that 32 cases are summarized whereas there were 34 operations. The two instances of a temporary return to normal chemical balance were in B. S., the patient with recurrent functioning carcinoma of the parathyroid who died of cancer and hyperparathyroidism, and E. G., the one patient with multiple adenomata, who was discussed in the last paragraph.

In addition to the above 32 cases of hyperfunctioning proved adenomata, we operated on one case of Milkman's syndrome, being at the time ignorant of the condition, and explored two cases of advanced renal disease with osteoporosis. At autopsy during this period of fourteen years three non-functioning oxyphile tumors were discovered, and two non-functioning parathyroid carcinomas were operated on by L. W. Sloan. In one the tumor suggested a carcinoma of the thyroid, in the other the tumor formed part of a cystic intrathoracic goitre. Both of these patients have died of other causes in no way connected with their parathyroid tumors.

There is no point in indulging in a complete statistical study of this series. Suffice it to say that our age and sex incidence is in accord with that quoted by Norris.[2] Our cases added to his, make it an even thing between right and left side as the site of the tumor. Seven of our tumors (namely 21.8 per cent) were in the upper mediastinum, but we have split the sternum in only one case, as the other upper mediastinal tumors could be reached and removed from above. However as our series grows it is probable that this procedure will have to be done more frequently.

The articles by Churchill and Cope[5] and by Cope[6] discuss the pathology and the surgical technique so adequately that there is no point in dwelling on these points other than to re-emphasize the necessity of exploring both sides to determine the total parathyroid equipment present. If a tumor is not readily found, the tracheo-

esophageal groove on both sides, the area behind the esophagus, and the upper mediastinum should be explored before resorting to splitting the sternum. In the article by Norris[2] 84 per cent of tumors were of the lower parathyroid, namely, the gland arising from the anlage in the third branchial pouch. The gland normally occupying the upper position in the adult grows from an anlage in the fourth pouch. In the third pouch is the anlage for the thymus and the lower parathyroid. As the thymus grows downward this parathyroid migrates with it and may go all the way to the depths of the anterior mediastinum or be dropped anywhere along the route, usually of course, stopping near the inferior thyroid artery from which it gets its blood supply. Cope[6] has pointed out that one can often find an atypically placed adenoma by following an anomalous branch of one of the thyroid arteries. In any case the surgeon must remember this embryological migration in planning his search in the neck, and the posterior as well as the anterior mediastinum.

The postoperative therapy has two objectives; first to maintain an adequate urinary output and, secondly, to control postoperative tetany. Oliguria or even temporary anuria may occur after operation, possibly because of the sudden shift in calcium excretion due to the drop in circulating calcium, which follows the sudden change in circulating hormones as calcium now moves back into the osseous system. There may be difficulty in taking enough water by mouth in the first 48 hours, so an intake of 3,000 cc. should be arranged for by supplementing the oral intake with intravenous fluid. Not over 1,000 cc. of dextrose in saline should be given in order to avoid NaCl retention, therefore, the major portion of the intravenous solution should be dextrose in water. In patients with severe decalcification a marked drop occurs in the circulating calcium well into the tetany level, in fact, one of our patients showed a drop to 4.9 mg. per cent. Therefore, such patients can be expected to exhibit a well-marked tetany and should be started on a prophylactic anti-tetany regime before tetany appears. The postoperative orders should include 5-10 gms. of calcium gluconate in the infusion fluid, and 2 cc. of parathormone to be given in the late afternoon. This regime is continued until the patient can take enough extra milk and cheese to provide the required amount of calcium. If tetany does supervene, AT 10, hytakerol, should be started after a few days to allow the parathormone

to be discontinued a week later. The administration of calcium must not be overdone, and only small amounts if any of viosterol should be given to avoid renal deposition of calcium. Usually the calcium level will be normal in at the most two or three weeks. After a month or two there will be no need for using AT 10 provided a normal blood calcium level has been present for a few weeks. Those with minimal decalcification may not exhibit any signs of tetany and will not require any treatment, so one can safely wait until tingling or a Chvostek sign appears before starting therapy. In our thirty-two cases there were twelve instances in which no symptoms of tetany appeared and therefore no treatment was required.

Hyperparathyroidism due to an overfunctioning adenoma of a parathyroid gland is a well-marked clinical entity that is curable by operation, as is shown by restitution of normal levels of calcium and phosphorus in the circulating blood that seem to be permanent, or at any rate persist as normal for years. If untreated the results are marked skeletal deformity and invalidism due to pain and weakness, with eventual death due to renal insufficiency. Diagnosis and operation prior to deformity and renal damage will prevent the appearance of these sequelae. It cannot be stressed too strongly that this condition be kept in mind in patients, even without renal calculi or obvious skeletal deformity, whenever any of the early symptoms characteristic of this condition are present and are not adequately explained on another basis. Only thus will earlier diagnosis be made, insuring an excellent result by avoiding the serious complications that otherwise are inevitable.

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THE THERAPEUTIC ROLE OF PROCAINE AND ITS DERIVATIVES*

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DURING THE 43 years that have elapsed since Einhorn announced the synthesis of p-amino-benzoyl-diethylamino-ethanol, the drug now known as procaine, it has become fully established as the most popular agent for local, regional and spinal anesthesia. Any drug with such wide usage is necessarily the object of many laboratory and clinical experiments designed to determine conclusively its pharmacological properties, its toxicity and to define its optimum use clinically. That the desired goal of such researches has not been achieved is now obvious from the considerable new material being added to our knowledge of procaine in the very recent past and at the present time. The most significant of these later experiments in both the laboratory and clinic are associated with the use of procaine administered intravenously.

Procaine was injected first into the veins of man 40 years ago.[1] This was done with a tourniquet in place and its object was to produce anesthesia of the extremities. The practice was soon abandoned. The present widespread use of intravenous procaine is a recent addition to therapy. It is readily understandable why intravenous procaine was so long avoided. Standard textbooks and other medical literature repeatedly pointed out the real danger of delirium, convulsions and death following the injection of procaine directly into the vascular system under any circumstances. There were numerous reports describing fatal convulsions in man after comparatively small amounts of procaine were inadvertently injected intravenously.

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In our laboratories (1940) procaine was given intravenously to anesthetized dogs during experiments undertaken to determine a means for protection against cardiac arrhythmias produced by injecting epinephrine.[2, 3] A definite protection was demonstrated and later similar results were observed in humans. This was substantiated during the war by Burstein when an opportunity was afforded for more extensive and better controlled observations in a busy army thoracic surgery center.[4] The administration of intravenous procaine in large amounts in the anesthetized patient was followed by successful attempts to use the drug therapeutically in unanesthetized individuals.[5, 6, 7]

It is now determined from extensive clinical observation that comparatively large amounts of procaine can be tolerated by man when given slowly by vein. With this knowledge intravenous procaine has been "tried" as a therapeutic agent for a surprisingly large number of unrelated clinical conditions. It has been used as an analgesic, for vasodilatation, to relieve muscle spasm, to diminish cardiac irritability and for an anti-histamine effect.

Clinical Application

The empirical application of intravenous procaine in clinical medicine has gained momentum without a well-defined fundamental basis for its action. This circumstance has occasioned a wide discrepancy in the reported results from its use. There is much speculation concerning the precise mechanism or mechanisms to explain the effects observed when the drug is administered as a therapeutic agent.

The essential action of procaine has been described as a direct one on the arterioles and capillaries with widespread dilatation. Although there is clinical evidence that peripheral circulatory dilatation occurs, conclusive experimental support in humans is lacking. Direct measurements of surface temperature should show an increase if capillaries in the skin are dilated. Our own efforts to establish this in man have given negative results. Dilatation probably could be produced if a large enough amount of procaine could be given intravenously. The serious toxic reactions to such doses constitute a barrier.

Graubard, Robertazzi and Peterson[8] gave procaine intravenously to relieve the muscle spasm of poliomyelitis. They were optimistic with the results and others have made similar observations. No explanation for this effect has been established.

There is ample clinical evidence that cardiac irritability is reduced with procaine applied topically to the myocardium or given intravenously.[2, 9] This effect is firmly established and is in accord with theoretical considerations in that there is a similarity in chemical configuration with quinidine, benadryl and other compounds which act as protoplasmic depressants upon the myocardium.

The anti-histamine action of procaine is not established by laboratory investigation although it has been successfully used to treat serum sickness.[10] This has been attributed to an anti-acetylcholine action. Harvey[11] has shown that procaine depresses the response of the terminal efferent fibers to acetylcholine and decreases production of acetylcholine at these sites. Conduction in nerve fibers may depend to some extent upon release and removal of acetylcholine, a process which is inhibited by the neutralizing action of procaine.

The reported analgesic effect of procaine given intravenously has provoked considerable speculation as to the mechanism involved. It has been suggested that it follows the leakage of procaine into the perivascular areas to reach the nerve endings through damaged capillaries. This can not be accepted until analysis of fluids at the site of injury are made. It was further suggested that analgesia may be the result of central action. This is supported by experiments on changes in pain threshold using the Hardy-Wolff-Goodell technique. Bigelow and Harrison,[12] using subcutaneous injections found a rise in pain threshold of about ⅓ of normal or the same range with therapeutic doses of acetylsalicylic acid. Using the drug intravenously, similar determinations were made here.[13] It follows that the clinical results reported are not consistent with the elevations of pain threshold observed. Either the concept of pain threshold is not so important in the evaluation of an analgesic drug, or the therapeutic benefits are the result of some other process.

In the wide use of procaine intravenously, more consistent agreement on its effectiveness has been demonstrated in the control of pain following trauma. There is general agreement that patients with fractures and other musculo-skeletal injuries experience less pain when procaine is administered.[8] In these groups are those with surgical trauma. Although this use of procaine has been established, it should be pointed out that pain syndromes of this nature have a wide individual variation and constitute a clinical group extremely difficult to evaluate in deter-

mining the effectiveness of analgesics. This is true also of the patients with pain from inflammatory reactions. In the latter group, optimistic results are reported in treating pain in the arthritides, neuritides and vascular disease. Considerable evidence has accumulated to warrant the use of intravenous procaine for burns, pruritus, and allergic skin reactions. Intravenous procaine has been used as an analgesic during parturition and for minor surgical procedures. One may say conservatively now that procaine may be an analgesic of consequence for patients with pain associated with trauma and inflammation. The favorable clinical application in other pain circumstances has not been established to the extent that it surpasses other means for effective therapy.

The evidence accumulated on the ability of procaine to correct alterations of cardiac rhythm is sufficient to establish it as the present drug of choice. This statement is qualified for the anesthetized patient only, since the amount needed in patients without the protection of anesthesia is too toxic for clinical usage. During anesthesia, procaine is of questioned prophylactic value, but finds its indication in the reversal of an abnormal rhythm. This should be further qualified to include the ventricular arrhythmias only. It is the firm conviction here that this latter use of procaine is more effectively accomplished when a single dose is given rapidly at the time its need is obvious. The aim is to provide the heart with an effective dose for a brief time during which irregularities of rhythm may be abolished.

Techniques

In efforts to determine the amount of procaine to produce maximum analgesia and other therapeutic effects, various recommendations have been made. In this regard there are two goals: to establish analgesia and to avoid aggravating or serious toxic reactions. Graubard and his associates[8] suggested a "procaine unit" calculated at 4 mgm./Kg. of body weight to be given in 0.1 per cent solution in isotonic saline in 20 minutes. Such calculations would be more accurate if obesity were not a factor and if they were determined by an accurate analysis of the rate of destruction of the drug. It is true that this calculated dose is tolerated without toxic manifestations and this may follow the fact that its destruction occurs in plasma at a rate almost as rapid as it is being administered. The clinical impression from the experience here is that effective intravenous procaine medication can be had by an amount

of the drug that continuously provides mild toxic manifestations. These include such symptoms as apprehension, metallic taste, slight nausea, vertigo and a feeling of warmth. If more serious symptoms of muscle tremors, delirium and convulsions are produced, the drug must be discontinued to avoid failure of the circulation and respiration.

Procaine may be administered to unanesthetized patients in 0.2 per cent solution for rapid effect and to avoid large amounts of fluid if this is desirable. The rate that it should be given is widely variable with individuals and must be determined with the criteria of effective analgesia in the light of mild toxic manifestations as a guide.

The most favorable effects in the treatment of arrhythmias in the anesthetized individual have followed the rapid injection of 100 mgm. of the 1.0 per cent solution.

Vitamin C is often given with intravenous procaine and many clinicians use the barbiturates for their prophylaxis against toxic reactions.

Mechanism of Action

Notwithstanding this vast accumulation of clinical experience with intravenous procaine, the mechanism of action, distribution in the tissues and its precise fate is still undetermined. It would seem that this fundamental knowledge should be available before the precise role of procaine in therapy can be determined accurately. Consequently a systematic study of the pharmacology of procaine has been undertaken in our laboratories. More detailed reports of these studies are available elsewhere but essentially the initial effort was to devise chemical methods for the identification of procaine and the products of its hydrolysis.[14] With these methods it was learned that an enzyme present in plasma was largely responsible for the almost instantaneous destruction of procaine to its metabolites, di-ethyl-amino-ethanol and para-amino-benzoic acid. In addition to establishing the manner of disposition of procaine in vivo, it was desirable to determine whether the observed toxic effects were associated with procaine itself or some product of its normal degradation. It seemed entirely possible that the therapeutic action of procaine could be exerted by a metabolite which was less toxic than the parent drug or if this were not the case, that procaine itself could be altered by chemical substitution in the molecule to make a more stable and effective drug.

In studies upon normal man, Brodie and his coworkers[14] demon-

strated that procaine is very rapidly hydrolyzed after intravenous administration and that urinary excretion is almost negligible as a method of disposition of the injected drug. Since 70 to 95 per cent of the para-amino-benzoic acid (free and conjugated) in procaine is recovered in the urine, it was apparent that this material was largely unaltered in the body. On the other hand, amounts of di-ethyl-amino-ethanol equivalent to 20 to 35 per cent of the original procaine can be isolated from the urine. When para-amino-benzoic acid and di-ethyl-amino-ethanol are injected as such, quantitative recovery in the urine is identical with that described when these substances are administered in the esterified form as procaine. It is evident, therefore, that the di-ethyl-amino-ethanol product of the hydrolysis of procaine is further metabolized in vivo in a manner as yet undetermined.

The fact that the concentration of procaine in the plasma does not increase with continuous intravenous administration while that of the alcohol metabolite does, as clinical effects are noted, suggests that the latter may be the pharmacologically active agent rather than the parent drug. The role of para-amino-benzoic acid has not been completely investigated, but the previously known behavior of this substance and the results of some few experiments offers little support for the possibility that it exerts many of the actions commonly attributed to procaine.

It seemed desirable, therefore, to investigate the pharmacological effects of di-ethyl-amino-ethanol upon man and laboratory animals. Observations early in the course of these studies indicated that the toxic effects were qualitatively similar to procaine, but large doses could be given intravenously before these were apparent. The margin of safety was significantly greater than with procaine. The relative lack of toxicity of this material and its greater flexibility with regard to dosage, pointed the way to a comparison with the orthodox actions of procaine. Comparisons were directed toward the properties which have been reported for procaine.

Di-ethyl-amino-ethanol Studies

Among the early efforts to compare the effects of the alcohol metabolite of procaine with the parent drug were those directed toward its ability to diminish cardiac irritability. This action which may be due to a protoplasmic depression of conductivity in cardiac muscle has been

studied in anesthetized animals and unanesthetized man. Di-ethyl-amino-ethanol is somewhat more efficient than procaine, although in larger doses, in reversing cyclopropane-epinephrine ventricular arrhythmias in the dog to sinus rhythm. The therapeutic benefit of the alcohol persists for longer periods than that produced by procaine. In unanesthetized humans the experience to date, although not extensive or conclusive, suggests that ventricular arrhythmias may be suppressed often when comparatively large doses of the alcohol (0.5 to 5.0 gms.) are given rapidly by vein. In another report, Rosenberg and his associates[15] describe 14 patients with ventricular extrasystole 13 of whom had normal rhythm after receiving di-ethyl-amino-alcohol. Another 8 patients with ventricular tachycardia were similarly treated with a restoration of pre-existing rhythm following in 6 of them. This effect on the specific tissues of the heart varies in duration. Similar results were unobtainable when attempts were made to treat supraventricular arrhythmias.

Di-ethyl-amino-ethanol has local anesthetic properties. Using local intracutaneous injections it was determined that the drug produced definite anesthesia for 20 to 30 minutes when a 10 per cent concentration was employed. No anesthesia was obtained when weaker solutions (1.0 per cent) were used.

The effects of di-ethyl-amino-ethanol upon the pain threshold were studied by a modified Hardy-Wolff-Goodell technique. Four grams of the drug given rapidly produced a definite, although slight, elevation of threshold. This elevation was within the range to be had with therapeutic doses of acetyl-salicylic acid and is inconsistent with clinical observations as is true with similar studies with procaine.

Skin temperature determinations were made before and after di-ethyl-amino-ethanol was given intravenously to determine vasodilatation in the skin and its actions upon smooth muscle. Amounts of 3.0 to 4.0 grams regularly produced an increase in skin temperatures of 3 to 9°C.[16] This definite effect was not repeated here with non-toxic amounts of procaine and suggests the alcohol more effective than the ester in overcoming vascular spasm.

The systemic analgesic effects of di-ethyl-amino-ethanol are similar to those that may be anticipated from intravenous procaine. The opportunities to complete significant studies have not been available during the short period the drug has been under observation. The early impression is that di-ethyl-amino-ethanol in relatively large doses is equally

efficient with procaine as an analgesic. It has the advantage of less troublesome administration and almost none of the toxic manifestations.

When toxic reactions from di-ethyl-amino-ethanol were observed they followed rapid injections of large amounts of the drug. These were similar to the mild reactions from procaine and are transient. Vertigo, slurred speech, a feeling of warmth, nausea and mild retching have occurred. Mild hypotension of short duration has also been determined. It is safe to say, however, that the serious toxic effects from procaine are not a hazard when its metabolite, di-ethyl-amino-ethanol is used therapeutically.

Summary

Intravenous procaine is now popular therapy for many unrelated clinical conditions. It is used for analgesia, for vasodilatation, to depress cardiac irritability and for an anti-histamine effect. The mechanisms for this variety of activities are unknown. Some of those suggested are discussed.

The technique for administering procaine intravenously is suggested.

One of the metabolites of procaine, di-ethyl-amino-ethanol has been used experimentally and clinically as a substitute for the parent drug. The results presently obtained from these studies are outlined.

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TREATMENT OF BELL'S AND OTHER PALSIES*

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THE loss of power of voluntary movement in a muscle or abnormalities of motions may be due to injury or disease of structures both within and outside of the nervous system. There are numerous and diverse causes of injury and disease of the nerve supply of a muscle which are responsible for the loss of its voluntary movement. Some of these causes are known; others are not. Ideally, treatment should be preventive, because by the time paralysis is evident many of the changes are irreversible. In some of the diseases characterized by the loss of voluntary muscle power, the etiologic factors continue to operate after the initial insult. In others, the period of activity of the causative factor is limited to a short space of time. In both of these circumstances and more particularly in the latter (if the individual survives) it is the residual symptoms which require therapeutic attention.

Until recent times, it was generally held that the afflicted individual was to be left alone while the body repaired the damages as best it could. During the past years, there has been abundant proof presented to indicate that treatment can exert a decidedly favorable influence, even though this treatment be symptomatic. These treatments can be divided into three types 1) operative, as in tendon transplants and arthrodeses, 2) mechanically supportive, such as the use of braces and crutches, and 3) measures grouped under the heading of physical medicine. The first two types of approach are generally applied relatively late in order to influence such residual difficulties as have not been favorably affected by measures included in the third category.

There are two relatively recent diagnostic procedures which have influenced therapeutic reasoning. One is improved electrical testing (chronaxie[1] and galvanic tetanus ratio[2]) and the other is electro-

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TABLE I—CHRONAXIES OF PATIENT MAKING EARLY RECOVERY

Frontalis	.17	Risorius	.16
Corrugator	.16	Orbic. Oris Lower	.09
Orbic. Oculi	.10	Orbic. Oris Upper	.15
Zygomaticus	.24	Triangularis	.16
Quad. Labii Sup.	.34	Mentalis	.24
Procerus	.14	Quad. Labii Inf.	.20

A case of Bell's Palsy of 13 days duration. Complete recovery in three weeks.

TABLE II—PROGRESSIVE CHRONAXIES OF PATIENT MAKING LONG DELAYED RECOVERY

	6/9	*8/6*	*12/17*	*3/18*	*6/11*
Frontalis	.30	4.0	.20	.11	
Corrugator	.23	4.0	.23	.17	
Orbic. Oculi	1.6	2.4	.30	.40	
Quad. Labii Sup.	1.0	2.3	.40	.60	
Procerus	.30	3.0	.44	.38	
Orbic. Oris Upper	1.0	2.0	3.4	2.0	.40
Orbic. Oris Lower	1.0	5.0	4.0	1.3	1.2
Mentalis	1.7	4.8	2.4	2.7	2.0
Quad. Labii Inf.	4.2	2.0	5.0	1.0	.80

myography.[3] Denervated muscles may show abnormal or completely absent potentials. On the other hand, intact neuromotor mechanisms can be detected by observation of small normal potentials even when voluntary movement be not discerned. Both of these diagnostic procedures also have prognostic value.

The absence of a voluntary motion can be due to difficulties other than damage to a motor nerve. Thus, the limitation of motion may be caused by a condition of hypertonus in the antagonists. For example, the inability to extend the leg may be due to overactivity of the hamstrings, rather than to weakness of the quadriceps.[4] Another possible factor is incoördination. The voluntary impulse is not directed to the desired muscle, but to some other which may indeed be the antagonist. A third factor appears to be due to the difficulty in formulating the concept of a motion after a period of inactivity. The occasionally observed rapid restoration of motion following directly upon the con-

ELECTROMYOGRAMS

OF APPARENTLY IMMOBILE MUSCLES

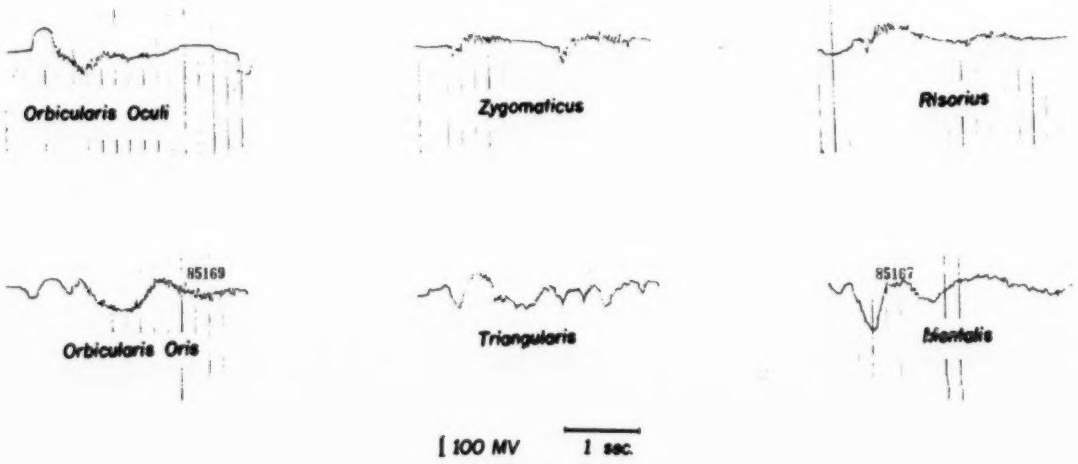

Figure 1

No voluntary motion visible, yet electromyograms indicated contractions of muscle fibres.

traction of a muscle by electrical stimulation might be explained on this basis—of the reinauguration of the pattern of the motion. A fourth factor is the presence of atrophic changes in muscles, bones, arthritic and periarthritic tissues. These changes may occur not only as a result of neural damage but also because of long periods of immobilization following injury or disease of skeletal structures. Under these circumstances motion becomes limited and painful. The patient follows the line of least resistance and desists from further attempts at mobilization. A fifth factor is the failure to recognize the possibility of motion even when the organic mechanisms for such activities are present. An injury or a disease may have made motion inadvisable or impossible for a period of time. With the passing of such temporary disability, the patient may continue in the belief that he cannot move the extremity. Correct medical advice or an intense emotional stimulus may then account for what would appear to be a "miraculous cure." At times the physician may be responsible for such a fallacious point of view—as illustrated by the patient with hemiplegia, the onset of which had occurred four months previously. She had been cautioned not to get out of bed because of her supposed inability to stand on her feet. A detailed functional examination revealed that the muscles of her involved lower extremities had adequate power to permit her to stand and to walk at first with assistance and shortly thereafter by herself. One or more of these factors may coexist in an extremity with a true paralysis of one or more muscles.

Much can be accomplished by skillfully guided exercises. Exercises are termed "passive" when the operator performs the entire movement and "active" when the motion is carried out by the patient himself.[5] There are three types of active exercises—which are referred to as "free," "assistive" and "resistive." When free movements are to be performed the influence of gravity should be reduced as much as possible to minimize resistance. This may be accomplished by immersion of the part in water (as in tanks and pools), by slings, or with smooth boards whose surfaces are powdered to diminish friction. Assistive movements are performed actively by the patient, aided by the operator or by gravity or by some outside force, for example, a weight and pulley. Their object is to permit the patient to accomplish more than he could unassisted. Resistive exercises are made more severe by the resistance offered by the operator, by gravity, or by weights and

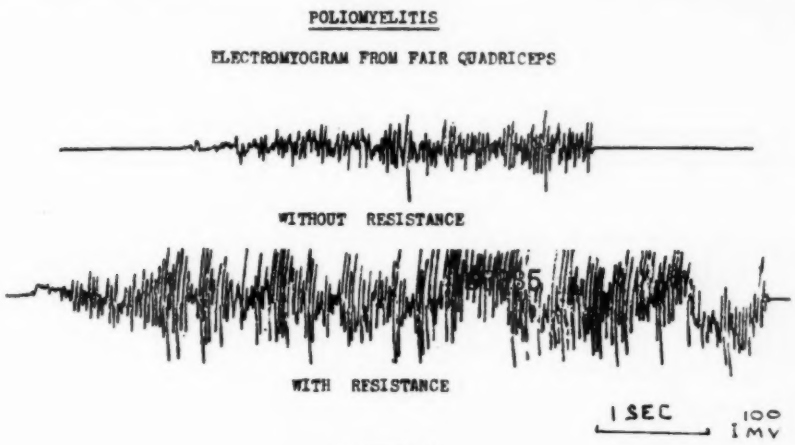

Figure 2A

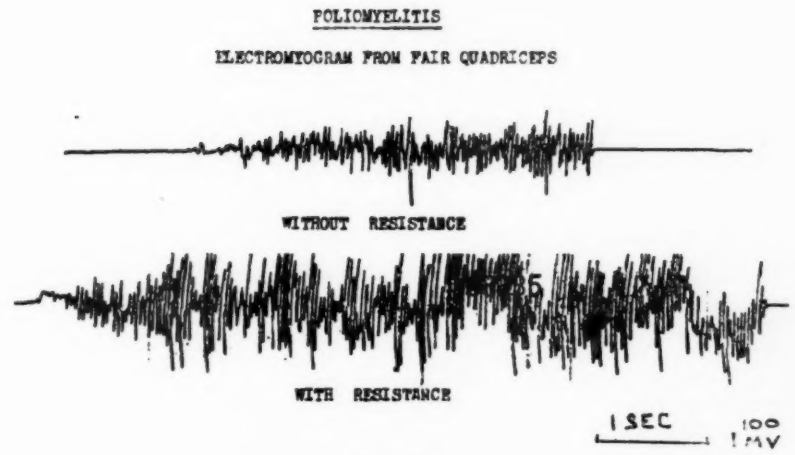

Figure 2B

apparatus. Effective exercises depend in large measure upon the motivation of the patient. He must realize that a desire to improve is essential and that such improvement depends upon his willingness to expend considerable muscular effort. When such correct motivation does not exist, psychologic as well as physical treatment is necessary. Of late, the emphasis has been placed on the use of resistive exercises as soon and as vigorously as possible.[6] Such emphasis appears valid as determined

by both clinical results and by electromyographic studies. These studies show that the use of resistance causes a marked rise in electromyographic potentials. This is due to the contraction of an additional number of muscle fibers.

In treatment of hypertonus, exercises are said to be made more effectual by the preliminary administration of certain drugs such as curare,[7] prostigmine,[8] or intravenous procaine.[9] The administration of exercise is based on an evaluation of the status of muscles as determined by functional, electrical and electromyographic testing. The scope of functional testing has been enlarged to include the examination of the patient's ability to perform the activities of every day existence. The integration of functional abilities with the movements required in the performance of vocational activities has made many an individual who would otherwise be completely dependent, into a self-respecting, completely or partially self-sustaining member of society.

Physical medicine is important because it can exert a favorable influence on the trophism of the structures whose normal well-being is dependent on intact neural mechanisms. Regeneration of nerves can occur—axis cylinders grow, and remyelinization take place. However, by the time the process of neural regeneration extends to the terminal end plates, the changes within the muscle, fibrous tissue, bone and joint structures may be so profound as to render them incapable of effective motion. It is the function of physical medicine to hold these atrophic alterations to a minimum. The necessity to do so is emphasized by the investigations of the changes produced by immobilization of the muscles of healthy young men. There occurred a deterioration in the mechanisms essential for adequate circulation, a decline in the basal metabolic rate, increased excretion of nitrogen, calcium, phosphorus, total sulfur, sodium and potassium, and a lowering of creatine tolerance.[10] The disturbances in calcium metabolism can be responsible for the occurrence of renal calculi and of myositis ossificans.[11]

Many of these considerations are exemplified in the treatment of peripheral paralysis of the facial nerve, commonly referred to as "Bell's palsy."

Treatment of Bell's Palsy

It appears to be the generally held idea that in as much as Bell's palsy is a disease from which the patient may recover spontaneously,

no effort should be made to treat him. This therapeutic nihilism might be justified on the basis that conclusive proof has not been presented thus far to indicate the possibility of exerting a specific influence on the diseased facial nerve. This attitude may not be completely defensible when one understands that there are two additional factors which merit therapeutic consideration. One is the alteration in the motor mechanisms responsible for the motions of the face which occurs secondarily to the interruption of the voluntary impulses. These secondary trophic changes in the facial muscles may prolong the period during which no motions are discerned, and may also be responsible for permanent disability. The other factor is the patient as a human being possessed of a psyche which can be tremendously disturbed when the victim realizes that his facial appearance has been altered profoundly and that in addition he now possesses some disturbing physical incapacities. The data which may indicate the reasonable possibilities of favorably influencing these two factors are both experimental and clinical.

Prevention of Stretching of Paralyzed Muscles. Ordinarily the muscles of both sides of the face contract simultaneously. It is questionable whether the muscles of the opposite side of the face relax completely when an effort is made at unilateral contraction. It is unfortunate for the sufferer from Bell's palsy that in every attempt at motion—as in talking, eating and registering emotion—the paralyzed muscles are pulled toward the uninvolved side. That such stretching is harmful is indicated by the experiments of Eisenhauer and Key,[12] who, working with the gastrocnemius-soleus group of muscles in cats, found that disuse atrophy is more marked in stretched muscles than in those maintained in the relaxed or neutral position. The clinical observations of Pickerill and Pickerill[13] are in accord with these experimental findings. These surgeons noted, that if means to prevent stretching of the muscles was applied directly after the purposeful cutting of the facial nerve in the removal of parotid tumor, the muscles lost surprisingly little tone during the three-week interval before plastic surgery (consisting of fascia lata and muscle grafts) was performed, in contrast to muscles where no such care was taken to avoid stretching. These workers believe that the cause of life-long disfigurement for many people lies in the generally held notion that because a large percentage of Bell's palsies recover spontaneously, treatment is not given to them. They, therefore, urge that "in every case of Bell's palsy the only safe

procedure is to presume that it will not recover unless something more than an attitude of masterful expectancy is adopted." It is their belief that "probably the chief factor in non-recovery of what should be the temporarily paralysed muscles is their immediate and continued overstretching by the non-paralysed muscles of the opposite side of the face." The Pickerill technique is to hold the muscles on the good side by fastening adhesive plaster from the skin on this side to the region of the mastoid process on the paralyzed side. The plaster glides over the skin of the involved side because of vaseline or oil applied to it. The paralyzed orbicularis oris muscle is held in a sling made by stretching adhesive strips from the region of the eyebrow down and across each other below the eye. This, they maintain, serves to hold the lid in apposition to the eye, to prevent epiphora, and to counteract the weight of the paralyzed cheek and so prevent the orbicularis muscle from losing tone.

Pracy[14] modified the Pickerill technique by having the adhesive which is stuck on the good side of the face extend to a wire loop which surrounds the mouth and is anchored by a "handle" going to and curving around the ear. This modification is designed to permit the more ready replacement of the adhesive when it becomes dirty or works loose and when it is removed to allow shaving.

The simpler and more commonly employed, though possibly not as effective procedure to counteract overstretching, is to hook a piece of covered wire around the corner of the mouth on the involved side. The other end of the wire is curved around the ear. This hook can be readily removed and replaced. A cosmetically better device designed for the same purpose is the removable intra-oral splint constructed by Allen and Northfield.[15]

Heat. It appears logical to apply a procedure to increase blood flow and to heighten the metabolism of muscles threatened with the atrophy which follows denervation. Local heating may well serve such purposes and also act as a preparation for whatever muscle contracting measures are deemed advisable. Experiments performed by Asmussen and Boje[16] showed that a given amount of work could be performed better, i.e., in a shorter time, when the organism was warmed up by preliminary work. Also a greater muscular tension could be developed when "warmed up" than when not. Passive warming up by diathermy or by hot baths also increased the capacity for work. The conclusion reached

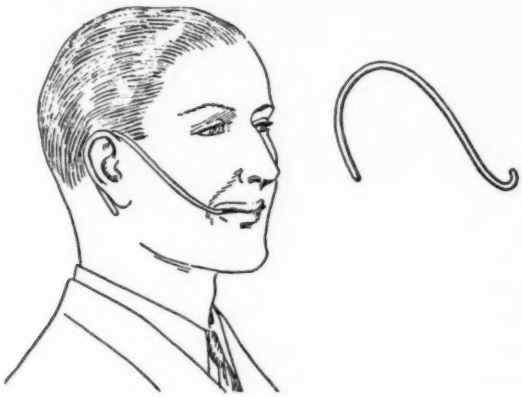

Figure 3—Wire splint for Bell's palsy.

from these results was "that a higher temperature in the muscles benefits the ability to perform work by accelerating the chemical processes in the muscles, probably also decreasing the intra-muscular viscous resistance."

All methods of heating are useful. A 1500 watt tungsten filament lamp has greater penetrating power than an infra-red lamp.[17] If the patient is photophobic (in spite of goggles—which cover the eyes only) the infra-red lamp is applied. Inasmuch as the facial muscles lie but a short distance beneath the skin surface, it is not essential to use the conversion heating of diathermy.

Electrical Stimulation. There has been a difference of opinion concerning the therapeutic value of electrical stimulation and the advisability of its use during the first ten days of paralysis. Much experimental work has been done. The preponderance of experimental evidence favors the early use of such stimulation in the treatment of denervated muscles. Thus, Kosman and his co-workers,[18] investigating the effect of electrical stimulation upon the course of atrophy and recovery of the gastrocnemius of the rat, found that the loss of weight and strength of experimentally denervated muscles can be effectively retarded by the use of electrical stimulation under the following conditions: 1) a current must be used which will produce maximal tension in the muscles within the limits of tolerance; 2) the muscle must be stimulated at frequent intervals; 3) treatment must be started soon

after denervation. Fischer and Ramsey[19] observed that the daily electrical treatment of denervated rabbit muscles is effective in retarding weight loss and the deterioration of muscle protein. Following some earlier experiments, Fischer[20] concluded that the best results are obtained when the electrical stimulation is started immediately after denervation and that the strength and the duration of the electrical current must be adapted to the changing excitability of the atrophying muscles. He postulated that the electrical treatment causes mainly a training effect in the denervated muscle similar to that in the normal muscle, which only increases the size of the fibers and their metabolic capacity. Suskind et al[21] reported that suitable electrical stimulation retards weight loss of denervated gastrocnemii in cats but exerts no effect on the contractile strength per unit of muscle. Kosman and his co-workers[22] found that the best type of electrical current for muscle stimulation is a 25 cycle sinusoidal one. Another modification of the electrical current can be employed for its mild irritating influence. This is the static brush discharge.[23] During its use, we have occasionally observed contraction of muscles on the paralyzed side of the face when the patient has been unable to make any such voluntary motion. The reaction may be like that which occurs reflexly as when a fly alights on the face. While the reflex arc is supposed to be interrupted in damage to the facial nucleus or to the peripheral nerve (in contrast to a supranuclear lesion) it may be possible that not all the fibers are involved, as can be frequently demonstrated for the motor component of the nerve by electromyography, and that similarly reflex activity may exist though to a diminished degree.

If the palsy persists after two weeks, we apply electrical stimulation to the muscles of the face, usually at intervals of every other day. This timing is made as a matter of convenience. Such stimulation can be administered earlier (from the very beginning of the paralysis) and more frequently. We have observed no harm with such a regimen when we have followed it. Experimental evidence would indicate the advisability of this procedure.

Positive galvanism is applied to a painful region when present. The pain usually disappears in a few days. It has not been proven that the galvanism influences the pain, though this is our impression.

Massage. The layman often thinks of massage as a measure to be used in the treatment of paralysis—an opinion which he shares with

some doctors. Massage, if used, should be applied to paralyzed muscles with very mild pressure—as in effleurage. In the face, particularly, where a bony surface lies but a short distance behind the muscles, there is danger of mechanical traumatization. There is warrant for the use of massage as determined by the experiments of Suskind et al[21] who found that massage causes only a slight retardation of the weight loss but proves to be effective in maintaining the strength of the denervated muscle. In massaging the face, the stroke should begin in the region of the chin and lip and proceed upward and outward to the area in front of the ear.

Exercise. Voluntary exercise is the most effective measure to improve muscle strength. However, the patient should not be requested to exercise a muscle until he has shown himself capable of producing voluntary motion in that muscle. In the care of Bell's palsy, extra caution is necessary because in the early stages of returning function the ability to cause unilateral movement on the involved side frequently is absent. In bilateral motion, the healthy side is the stronger and the weak muscle is in danger of being stretched. This danger may not be as great when the frontalis and orbicularis oculi show motor power and the patient is instructed to wrinkle his forehead or close his eye, as it is when he is requested to show his teeth. In the latter instance, it may prove helpful to have the patient manually restrain the activity of the muscles on the uninvolved side of the face while exercising the muscles on the paralyzed side. The patient should preferably exercise in front of a mirror and follow specific instructions.

General Therapeutic Considerations. The patient will frequently ask questions in addition to those concerning diagnosis and prognosis. These should be answered. He is told to avoid eye strain—as in reading and in looking at motion pictures. Some are helped by the wearing of colored glasses or an eye shield, particularly if there is marked ectropion. Washing with boric acid solution will help allay irritation of the eye. Chewing can be done on either side of the mouth, inasmuch as the masseter and buccinator muscles are not involved, but the patient may prefer to do most of it on his good side because food collects between the teeth and cheek on the paralyzed side. Some patients find that they can chew best when they use their hand to pull the involved cheek upward toward the ear. The answer to the question "Shall I go to work?" depends on the nature of the work. The preoccupation of activity is

best—if it be not the type which requires constant use of the facial muscles—as in talking. When talking is necessary, it should be done "through the teeth" as it were, and with a minimum of facial expression. Drafts are to be avoided.

Other Methods of Treatment. According to Feiling,[24] little effect can be expected from drug treatment, but it is perhaps of some value to prescribe a mixture of iodides with salicylates. Equally questionable is the more recent use of vitamin B. Sedation may be indicated for pain.

In 1919 Leriche advocated resection of the superior cervical ganglion as a method for treating early peripheral facial paralysis. Later he considered that infiltration with a local anesthetic was superior to ganglionectomy. More recently Arnulf[25] injected the stellate ganglion at intervals of every second or third day at first, and later once a week. He explains his results, which he states are good in early cases, on the basis of vasodilatation of the vasa nervorum.

Psychic Considerations. Too often the doctor loses sight of the fact that his patient is a human being, possessed of the hopes and fears engendered by his intellectual and emotional reactions. It may not appear to be as catastrophic to an old man as it is to a young woman in her twenties to awaken one morning and find one side of the face distorted and incapable of function. To be informed that "it is not a stroke" gives some degree of reassurance, which soon passes in the further recognition of finding oneself in a state which still appears calamitous. The advice to "leave it alone for the next ten days because it may get better of itself" gives a dubious sense of comfort which disappears entirely when, as in many instances, the paralysis is still present at the end of that time. This approach is wrong because immediate treatment is necessary and because a more definite therapeutic attitude has far more reassuring value. If, as it should be, the patient's face is closely scrutinized at every visit, slight evidence of improvement may be detected. There may be a diminution of distortion when the face is at rest, the naso-labial fold may become evident; lines may appear beneath the eyes or under the lip; the corner of the mouth may deepen and there may be a flicker of a contraction here or there. Description of this encouraging objective information as well as that gleaned from chronaxie studies and from electromyography gives additional help to the patient's morale. These little signs permit the physician to say the condition is improving, and what reassuring words these are. With this approach,

the patient may, in large measure, be saved from the torturing fears and doubts during the period of the palsy. The immediate treatment of Bell's palsy is very important as indicated by experimental and clinical evidence. However, if this treatment did nothing more than minimize psychic trauma there would still be sufficient reason for applying it immediately and at regular, frequent intervals.

A physician patient described his own mental reactions as follows: "For the first week or two when the condition is at its worst, one has a sense of complete frustration and uselessness because of the impossibilities of closing one's eye, of spitting, drinking, smoking, washing the mouth, and most depressing, the impossibility of speaking properly or of smiling. These thoughts dominate your life during waking hours, and also when kept awake at night by pain in the region of the mastoid. While your mind is deeply occupied by professional activities, you forget about your trouble temporarily, but otherwise you begin early in the morning on washing, shaving, cleaning your teeth, when you cannot avoid noting the grotesque appearance of your face and the impossibility of helping it. Even during professional duty hours, you feel down in the dumps because you cannot speak freely to patients and especially difficult are telephone conversations."

The clinical results should, of course, be the final determinant of the value of the treatment of Bell's palsy. Table III shows the duration of the disease in 100 patients who presented themselves for treatment within two weeks of the onset of their paralysis. Fifty-five of these are classified as Group "A" and 45 as Group "B". The patients of Group "A" were treated daily during the first two weeks (with the exception of Sunday) with radiant heat and the static brush discharge. Those who still showed signs of paralysis after these two weeks were treated with radiant heat and interrupted galvanic current three times weekly. The patients in Group "B" were treated usually every other day. Their treatment consisted of radiant heat and massage during the first two weeks. Subsequently, interrupted galvanic stimulation and exercise were administered three times a week. The members of both groups were given a supporting device consisting of a curved wire hooked into the corner of the mouth and over the ear.

It is interesting to observe that 40 per cent of the Group "A" patients were discharged at the end of two weeks of treatment, while only 20 per cent of Group "B" were recovered at the end of the same

TABLE III—DURATION OF PALSY: RESULTS ACHIEVED IN 100 CASES

Number of Cases	%	*Total %*	*Weeks*	*Number of Cases*	%	*Total %*
2	4		1			
20	36	41	2	9	20	
4	7		3	5	7	
13	24	71	4	5	11	38
2	4		6	3	7	
2	4		7	3	7	
			Months			
5	9		2	7	15	
2	4	92	3	2	4	71
1	2		4	6	14	
2	4		5	1	2	
2	4	100	6	2	5	92
			7	1	2	
Group "A"—Patients treated daily with			8	1	2	
Splinting, Radiant Heat and Static			9	1	2	
Brush Discharge.			11	1	2	100

Group "B"—Patients treated every other day with Splinting and Radiant Heat.

time period. At the end of a month 71 per cent of Group "A" and 38 per cent of Group "B" required no further treatment. After three months 92 per cent of Group "A" and 71 per cent of Group "B" were judged as needing no further care. The remaining 8 per cent of Group "A" continued to receive treatment during the following three months, at the end of which time the patients were discharged even though some residual weakness persisted. The termination of this additional three month period (a total of six months) still found 8 per cent of Group "B" requiring care which was continued for another five months. These findings clearly indicate that patients receiving daily treatment during the first two weeks with heat and static brush and subsequently interrupted galvanic stimulation do better than those whose initial therapy was heat and massage applied every other day and then interrupted galvanic excitation.

Not all patients make a complete recovery. In a few, some residual weakness may continue for a long time. A complication which occurs in cases of long standing is contracture. These patients may show a

narrowing of the palpebral fissure, deepening of the naso-labial furrow, and of the lines at the corner of the mouth. They may complain of a sensation of tightness in the muscles of the face and may experience intermittent muscle spasm. Feinstein[26] considers the contracture as due to a fibrous metaplasia inasmuch as there were numerous areas of electrical "silence" in the facial muscles when electromyographic examinations were made.

Another annoying sequel is the inability to contract individual muscles after the return of motor power. The muscles may move in groups. The associated movements were accounted for on an anatomical basis by Howe, Tower and Duel[27] who found that many of the regenerating axons do not follow their original pathways and dichotomization of the axons is frequent. More recently Weiss and Edds,[28] on the basis of studies on incompletely denervated muscles in laboratory animals, concluded that spontaneous recovery is due to the fact that intramuscular branches of the intact motor fiber undergo additional branching and take over the supply of denervated muscle fiber. This occurs only when intact and denervated elements lie intermingled. The ultimate prognosis for the independent movements of the facial muscles is poor in view of this abnormal pattern of innervation.

Several surgical methods of treatment have been recommended for persistent palsy. These include anastomosis of the facial nerve with some other nerve in the neck; direct line repair utilizing a branch of the anterior crural, and the uncovering of the nerve in the Fallopian aqueduct followed by its decompression by incision of the sheath.[29, 30] Plastic repair has also been advised with fascia lata and muscle grafts and with tantalum wire or ribbon.[31] A critical comparison of the results obtained by surgical means and by prolonged conservative treatment remains to be made.

Summary and Conclusion

Experimental and clinical evidence has been presented to indicate the importance of the early application of the measures employed in physical medicine in the treatment of Bell's and other palsies.

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RECENT ADVANCES IN THE DOMAIN OF THE ANTI-HISTAMINE SUBSTANCES: THE PHENOTHIAZINE DERIVATIVES*

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WE HAVE studied recently a new series of anti-histaminics. Chemically they are derivatives of phenothiazine. The most active of the series is N-dimethylamino- 2-propyl-I-phenothiazine. The anti-histamine properties of this synthetic substance were discovered in France in 1946[1] and have been intensively studied there since.

HISTORICAL SURVEY

The first synthetic substance reported to possess anti-histamine properties was described by Fourneau and Bovet in 1933[2] and later by Staub and Bovet.[3] This was 929 F or thymoxyethyldimethylamine. In 1937 Bovet and Staub[4] also described 1571 F a derivative of ethylene diamine. Both these substances showed only moderate activity and were too toxic for therapeutic administration.

In 1942 Halpern[5] showed that N-dimethylaminoethyl-N-benzyl-aniline (Antergan or 2339 RP) was more powerful and less toxic than the earlier products and the first clinical trials were attempted.

During the years which followed, various modifications of Halpern's drug were produced, such as Neo-antergan (Bovet and Walthert, 1944[6]), Benadryl (Loew, Kaiser and Moore, 1945[7]) and Pyribenzamine (Mayer, Huttrer and Scholtz, 1945[8]). Numerous comparative studies have been made, notably by Code[9] and by Feinberg,[10] as well as the many studies on the experimental activity of each substance separately.[11, 12, 13]

In 1946, Halpern and Ducrot[1] showed that certain phenothiazine derivatives possessed anti-histamine properties which were in many respects more powerful than those of any previously described sub-

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stance. A series of experiments was made to study the activity of this new group of substances, particularly N-dimethylamino-2-propyl-I-phenothiazine, known as 3277 R.P. or Phenergan.[14]

Experimental Findings

Phenergan possesses the same well-established properties as the other anti-histamines, but quantitatively its action is much more powerful in many respects.

1) The antagonism of Phenergan to histamine is well shown in experiments on the smooth muscle of the bronchi, intestine and uterus and by its inhibition of the Triple Response of Lewis and of the histamine effect on the blood pressure.[5, 7, 15, 16]

The degree of protection against histamine conferred by Phenergan, is much greater than that given by any other anti-histamine substance. A dose of Phenergan of 20 mgm. per kilo protects the guinea pig against 1,500 and the rabbit against 450 lethal doses of histamine.

2) The anti-anaphylactic effect is equally striking. Phenergan counteracts anaphylactic shock and prevents the Prausnitz-Kustner reaction. This action is much greater than that of the other anti-histamine substances.

3) The duration of action of Phenergan is much prolonged. For example, the duration of action against experimental asthma in the guinea pig is 3 times as long as the action of Antergan or Neo-Antergan under the same conditions.

Studies made in man[17] by following the intradermal histamine response after oral administration of various anti-histamines have shown that the duration of action of Phenergan is quite remarkable in the slowness with which it disappears.

4) Phenergan, like the other anti-histamine substances, cannot, however, counteract the effect of histamine on the secretions. Hence, animals given large doses of histamine after the administration of Phenergan show no immediate signs produced. This probably explains the constant appearance of gastric ulceration under such conditions.[18]

5) Last and Loew (1947)[19] had already demonstrated by Menkin's method that Benadryl and Neo-Antergan counteract the local increase of capillary permeability induced by histamine. By noting the penetration of fluorescein into the anterior chamber of the eye[20, 21] and by the diffusion of dyes into peritoneal exudates it has been shown that Phen-

ergan powerfully opposes the increase of capillary permeability produced by histamine and various other substances.

6) Two special effects of Phenergan, possibly due to its more powerful action on capillary permeability have been investigated.

a) Phenergan prevents the appearance of the acute pulmonary edema, which is induced in unprotected animals by intravenous epinephrine[16] or by certain poison gases, such as chloropicrin or phosgene.[22]

b) Phenergan prevents the induction of experimental orthostatic albuminuria in rabbits.[23]

7) Phenergan has shown in various functions a non-negligible atropine-like activity.

Clinical Studies

Methods: Phenergan was administered orally in the form of 25 mgm. tablets. The usual dose varied between 25 and 100 mgm. daily, but in certain cases, up to 200 mgm. were given. Blood counts were carried out before and every two weeks during treatment. Allergic clinical and skin tests were carried out before and during treatment whenever possible.

Results: a)—*Serum sickness.* Seventeen cases of serum sickness were treated. In each case the skin manifestations, such as pruritus and urticaria, disappeared within from 30 minutes to 3 hours after administration of the drug. Joint pains were present in four patients and disappeared under treatment in only two of the cases. The fever was scarcely influenced.

b)—*Urticaria.* One hundred and twenty-three cases of urticaria of varying origin have been treated. In only twelve of these cases could an allergic basis be demonstrated by clinical and cutaneous tests.

One hundred and eight cases (87.8 per cent) showed immediate improvement. The pruritus was the first symptom to disappear; then the skin reaction tended to diminish and had often entirely disappeared after a few hours. Of the remaining fifteen patients, six showed signs of intolerance and were unable to continue treatment, while nine cases were little, or not at all, benefited by the drug. All the cases of definitely allergic origin improved under treatment, but among the successes were several cases in which there was no reason to suspect any such cause. About 60 per cent of the successful cases had previously failed to respond to Neo-Antergan.

c)—*Angioneurotic edema.* Out of nineteen cases of angioneurotic edema, only three were not improved by treatment (84 per cent of favorable results). Two of the successful cases were patients in whom edema of the lips had persisted in between the acute exacerbations.

Apart from these cases of true angioneurotic edema, there were two patients who suffered a local edema after the slightest pressure on any part of the body. These cases were uninfluenced by Phenergan.

d)—*Pruritus.* Out of 18 cases of prurigo from varying causes, six were not influenced by Phenergan, but 12 were vastly improved, the pruritus ceasing even when the visible lesions persisted unchanged. Included in these 12 are several cases of pruritus due to scabies.

e) *Eczema.* None of our seventeen cases of chronic eczema was completely cured by treatment. In a few cases slight relief was obtained, especially from the subjective symptoms such as pruritus.

Out of twenty-two cases of acute eczema and contact dermatitis, three showed rapid improvement which ended in complete cure. The rest of the cases improved only after a much longer period and it is difficult to assess the influence of Phenergan on these results.

Three cases of arsenical and one case of gold erythrodermia showed no real improvement on treatment with Phenergan.

f)—*Allergic purpura.* One case of allergic purpura, in which new crops of petechiae appeared daily for three weeks before treatment, was treated with Phenergan. Administration of the drug was followed by immediate cessation of fresh eruptions.

g)—*Hay fever.* One hundered and forty-two cases of hay fever were treated between the spring of 1947 and that of 1948; ninety-eight cases (69 per cent) showed complete disappearance of all signs and symptoms; thirty-six cases were only partially relieved; the sneezing ceased but the nasal congestion remained more or less the same; eight cases were completely unchanged by treatment but most of these were unable to tolerate full doses of the drug.

It should be noted that, in the majority of cases, 25 mgm. of the drug daily suppressed sneezing, but a dose 4 to 6 times as great is usually necessary to give complete relief from all the symptoms. For a few patients, however, 6-12 mgm. daily sufficed to suppress all symptoms.

At a recent meeting of the French Society of Allergy (June 15th, 1948) Pasteur Vallery-Radot, Blamoutier and B. N. Halpern have com-

municated statistics of 200 cases of hay fever treated with Phenergan with a dose of 25 mgm. to 50 mgm. daily; they reported 86 per cent of excellent results with relief of all symptoms; in only 14 per cent the improvement was incomplete.

h)—*Asthma.* Seventy-two cases of asthma were treated but an allergic basis could only be demonstrated in 9 of them. In all these 9 cases, considerable relief or even complete disappearance of the asthma was obtained. In 21 other cases without any appreciable allergic origin, there was a certain degree of improvement. In the remaining 42 cases, the results were completely negative.

i)—*Spasmodic cough.* Nine cases of spasmodic cough were entirely uninfluenced by treatment.

j)—*Migraine.* Out of twenty cases of migraine, six were improved by Phenergan.

It was impossible to determine an allergic basis for any of these 6 cases.

k)—Phenergan appeared to have no effect on chronic or subacute rheumatism or on acute glomerulo-nephritis. It did not seem to influence the allergic manifestations of tuberculosis, or the intradermal tuberculin test. This latter observation is in contrast to its action on allergic skin tests for other diseases. In such cases, whenever skin tests were found to be positive before treatment, immediately after adequate dosage with Phenergan they became temporarily negative.

Tolerance and side-effects. The drug was usually well tolerated. In particular, it did not provoke the digestive upsets which often occur with the other anti-histamine substances.

The blood picture was affected in only two cases, a slight neutropenia being observed. Administration of the drug was immediately stopped.

The only important side-effects were of nervous origin. About 25 per cent of the patients showed a certain degree of drowsiness accompanied by vertigo and instability when standing upright and by sensations of drunkenness. Occasionally there was also a slight decrease in intellectual power. In rare cases, insomnia occurred rather than drowsiness.

These troubles, which are impossible to predict and which may occur even with feeble doses, constitute the most serious disadvantage to the use of Phenergan. Usually they seem to be partially neutralized

TABLE OF RESULTS

Condition	*Total No. Treated*	*Cure*		*Improvement*		*Failure*	
		Actual No.	*%*	*Actual No.*	*%*	*Actual No.*	*%*
a. Serum sickness	7			7	100	0	0
b. Urticaria							
1/Def. allergic	12	← 12 →			100	0	
2/Aet. unknown	111	← 96 →			86.5	15	13.5
Total	123	108			87.8	15	12.2
c. Angioneurotic edema	19	0	← 16 →		84	3	16
Pressure edema	2			0		2	
d. Pruritus	18	← 12 →			67	6	33
e. Eczema							
1/Acute & contact	22			3	13.6	19	86.4
Chronic	17			0	0	17	100
Total	39			3	7.7	36	92.3
2/Erythrodermia gold and arsenic	3	0		0	—	3	100
F. Allergic purpura	1	1					
g. Hay fever	142	98	69	36	25.3	8	5.7
h. Asthma							
1/Def. allergic	9	← 9 →			100	0	
2/Aet. unknown	63	0		21	33.3	42	66.6
Total	72			30	41.7	42	58.3
i. Spasmodic cough	9	0		0		9	100
j. Migraine	20			6	30	14	70

K. Other conditions—Acute and subacute rheumatism, tuberculous allergy, acute glomerulo-nephritis—uninfluenced.

by the simultaneous administration of Benzedrine. Moreover, the nervous troubles almost always disappear within a few days, even if treatment is continued with the same dose.

The drowsiness may be neutralized if Phenergan is given at night. This effect wears off before morning but the true action of the drug continues throughout the following day.

Discussion

The experimental and clinical results described above lead us to consider Phenergan as a powerful anti-allergic substance. However, several conditions in which no allergic cause could be demonstrated, were influenced by the drug. These were:

a) Experimental syndromes such as acute pulmonary edema due to epinephrine or poison-gas; orthostatic albuminuria;

b) Clinical cases of migraine, certain skin conditions and some asthmas. On the other hand, a certain number of definitely allergic conditions were not benefited by the drug; for example, all chronic and most acute cases of eczema.

In consequence, the problem of the mechanism of action of Phenergan still has to be elucidated. The first theory was that histamine is responsible for non-allergic syndromes influenced by Phenergan. Up to the present there has been no serious proof of this. The experimental work described above suggests that Phenergan acts on capillary permeability. In this connection, it is very striking that most of the pathological conditions controlled by Phenergan are characterized by serious extravasation through the capillary wall, for example, experimental acute pulmonary edema and orthostatic albuminuria, urticaria and even, perhaps, migraine.

Summary

1) Experimental work on Phenergan, a phenothiazine derivative which is a powerful new anti-histamine substance, is described. Apart from its action on allergic conditions, it prevents the production of experimental acute pulmonary edema and orthostatic albuminuria.

2) Clinical trials with this substance proved it to be of value against serum sickness, urticaria, angioneurotic edema, hay fever and allergic purpura.

Less success attended the use of Phenergan in cases of asthma, migraine and pruritus, with almost none against the eczemas.

3) The mechanism of action of Phenergan is discussed. The experimental and clinical evidence is in favor of its action on capillary permeability.

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